DISSERTATION

FUNCTIONALIZATION OF PYRIDINES AND OTHER AZINES VIA PHOSPHORUS LIGAND-COUPLING REACTIONS

Submitted by

Michael C. Hilton

Department of Chemistry

In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Fall 2019

Doctoral Committee:

Advisor: Andrew McNally

Melissa Reynolds
Debbie Crans
Tai Montgomery

Copyright by Michael C. Hilton 2019

All Rights Reserved

ABSTRACT

FUNCTIONALIZATION OF PYRIDINES AND OTHER AZINES VIA PHOSPHORUS LIGAND-COUPLING REACTIONS

Nitrogen heterocycles are ubiquitous in pharmaceutical compounds with pyridine being one of the most frequently occurring examples. The discovery and development of new drugs rely heavily on our ability to modify these commonly occurring structures. The functionalization of pyridine has a long history but despite this, there remain some deficiencies in this area of synthesis. Reactions which expand upon the known methodologies are of tremendous value to medicinal chemists who frequently work with pyridines and similar azines.

Chapter one will cover the relevance of pyridines in pharmaceuticals and will explain how structural features contribute to their presence in drugs. Conventional and newer methods to functionalize pyridine are also addressed. Chapter two will describe the work of the McNally lab in the development of heterocyclic phosphonium salts as reagents to selectively functionalize pyridines. An application of these salts is as precursors to form C–O bonds from alkoxide nucleophiles.

Chapter three presents the development of a strategy to construct bis-heterobiaryls using phosphorus ligand-coupling. This method offers an alternative to the widely used metal-catalyzed approaches which often struggle in the synthesis of bis-heterobiaryls. Lastly, chapter four will expand upon this work showing a new approach to prepare bis-heterobiaryls using heteroaryl halides. This route enables easy access to 2,2'-bipyridines which are difficult to synthesize using conventional methods.

ACKNOWLEDGEMENTS

I would like to thank Dr. McNally for the opportunity to work on interesting and impactful problems during my graduate studies. Through Andy's training and guidance, I have developed into the chemist I am today. I would also like to thank Dr. Reynolds, Dr. Crans, and Dr. Montgomery for being on my committee and spending their valuable time providing feedback during this process.

My path through graduate school was not a lone journey and for this reason, I would like to thank the other McNally group members. I am most appreciative of Ryan Dolewski, Ben Boyle, and Xuan Zhang, who I worked with the most over the last five years and have greatly contributed to me improving as a chemist. As for Kyle Nottingham, Chirag Patel, Patrick Fricke, Ryan Anderson, Luke Koniarczyk, Jake Greenwood, Jeff Levy, and Ren Rong, it was a pleasure to know you all.

Lastly, I would like to thank my friends and family who were incredibly understanding and supportive during my time in graduate school. I am especially grateful to Danielle Klaus who came with me from Missouri and has been an important part of my life. While I am glad that my time in graduate school is coming to an end, I am very appreciative of the opportunities it has enabled and the people that I got to meet along the way.

TABLE OF CONTENTS

CHAPTER ONE

The Relevance of Azines in Pharmaceuticals and Methods of Functionalization

1.1 Occurrence of Electron-Deficient Nitrogen Heterocycles in Drug Compounds

Electron-deficient nitrogen heterocycles are some of the most common motifs found in drug compounds. In a 2014 survey of FDA approved small molecule drugs, pyridine was found to be the second most common nitrogen heterocycle with 62 unique examples out of a total of 1035.[1] Only piperidine with 72 examples was featured in more drugs. Other common electron-deficient nitrogen heterocycles include pyrimidines, pyrazines, quinolines, and quinazolines which account for a combined 37 examples (**Figure 1.1**).

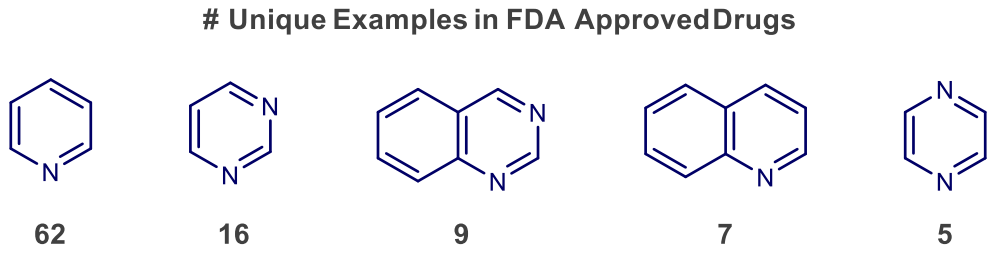


Figure 1.1: Occurrence of Electron-Deficient Nitrogen Heterocycles in Pharmaceuticals

These heterocycles are present in some of the most well-known drugs on the market (**Figure 1.2**). Claritin, Lunesta, and Nexium, which are household names, and all feature a pyridine.[2] Velcade[3] and Tasigna,[4] which are both cancer treatments, contain a pyrazine and pyrimidine, respectively. Ibrance, a treatment for breast cancer and one of the top-selling drugs in 2018, has multiple azines within its structure.[5]

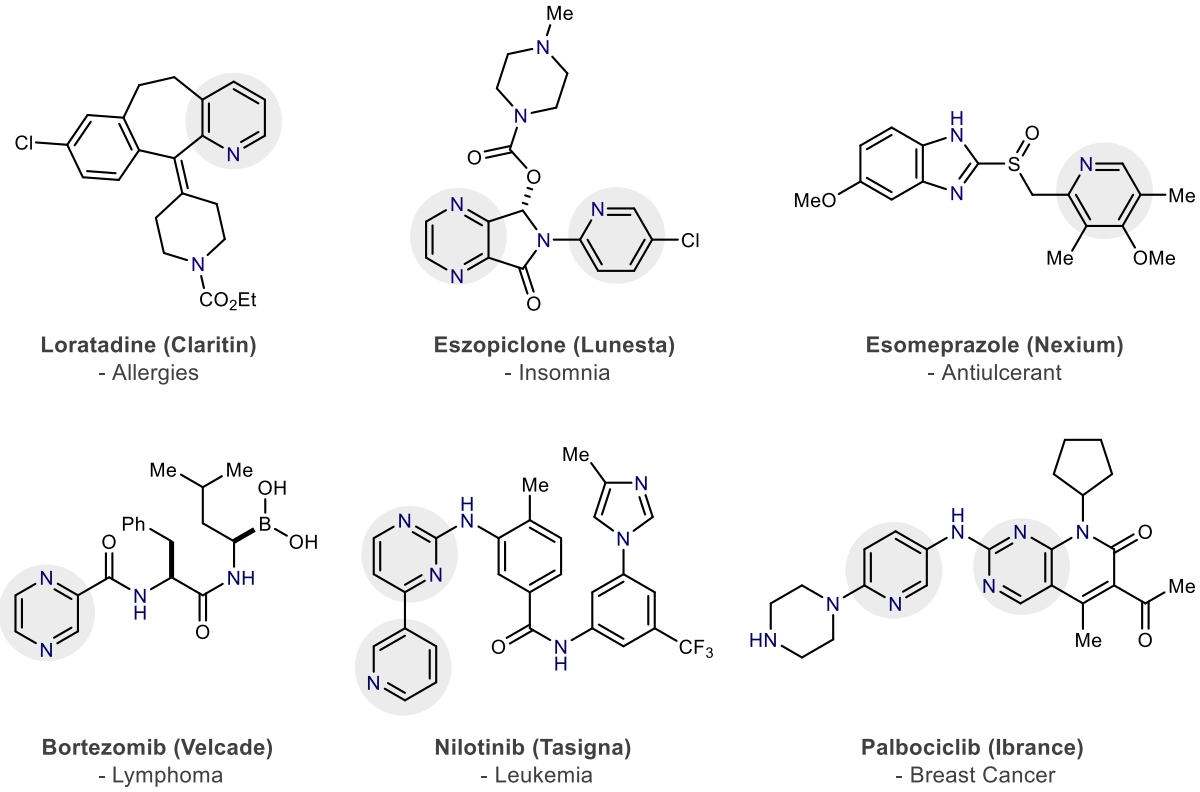


Figure 1.2: Pharmaceuticals Featuring an Electron-Deficient Nitrogen Heterocycle

1.2 General Properties of Pyridine

Heteroaromatics, a subset of heterocycles, are aromatic compounds with at least one heteroatom (non-carbon atom) incorporated in the ring. When the heteroatom is nitrogen this can have a pronounced effect on the properties of the aromatic ring and this is best illustrated by comparing benzene and pyridine.[6] Nitrogen is significantly more electronegative than carbon, and consequently the π-system of pyridine has less electron density. Additionally, the nitrogen lone pair is orthogonal to the π-system and thus cannot donate electrons into the ring. A greater amount of electron density is weighted towards the nitrogen atom causing pyridine to have a dipole moment of 2.2 D. The electron density of benzene, on the other hand, is evenly distributed within the ring and thus the ring has no dipole moment.

The reactivity of pyridine is also influenced by the presence of the electron-withdrawing nitrogen which causes the π system to be less reactive towards electrophiles when compared with benzene and electron rich arenes such as phenol or aniline (**Figure 1.3**).[6] Pyridine can react though the π-system via electrophilic aromatic substitution but generally requires harsh conditions (vide infra). Another important consequence of the nitrogen is that it makes the 2- and 4-positions electrophilic and thus nucleophiles can add into the ring.[7] Examples of this reactivity include the Chichibabin and nucleophilic aromatic substitution (S_NAr) reactions which will be discussed later in this dissertation. Lastly, the orthogonal lone pair of the nitrogen can enable pyridine to act as a Brønsted or Lewis base.

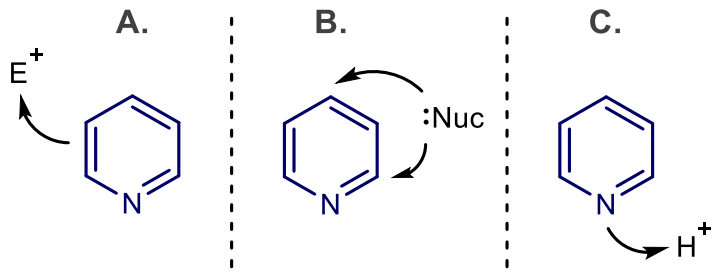


Figure 1.3: Reactivity of Pyridine as A) π-nucleophile B) electrophile C) base

1.3 Influence on Drug Design

Pyridine and other electron-deficient nitrogen heteroaromatics can have a large influence on the pharmacodynamics and pharmacokinetics of a drug. These heterocycles affect the solubility of a drug, its metabolism in the body, and lastly its ability to bind to a specific target. The aqueous solubility of a drug can impact on the oral absorption and the rate which it is taken into the body.[8] A drug which is too hydrophobic will have a low concentration in the bloodstream and thus will be poorly circulated throughout the body requiring higher dosing.

Addition of polar functionality will increase the hydrophilicity of the compound making the drug more water soluble. Pyridine and other nitrogen heterocycles can be incorporated onto a drug scaffold for this purpose.[9]

A common way for the body to remove a drug is through its oxidation to a more polar intermediate which is easier to excrete. This process generally involves CYP450 enzymes which can introduce polar hydroxyl groups making the drug more water soluble.[10] Drugs with electron-rich aromatics are more susceptible to this process and thus will be removed from the body at a quicker rate. To slow the rate of metabolism, electron-deficient aromatics such as pyridine can be used instead.[9]

Nitrogen heterocycles can also be incorporated onto drugs to influence its binding to a biologic target. The lone pair on the nitrogen can serve as a hydrogen bond acceptor in this regard, allowing for binding to the polar functionality commonly found in drug targets. An example of this can be seen in **Figure 1.4** with Gleevec where the nitrogen atom of pyridine hydrogen bonds with a specific methionine present in the Abl kinase.[13] In addition, ring systems can improve selective binding by filling a hydrophobic pocket within the enzyme.[11] In the example with Gleevec, the pyridine and pyrimidine serve this purpose through hydrophobic interactions with the enzyme. An additional benefit of a ring system is that it provides rigidity, limiting possible conformations to allow for more selective binding.[12]

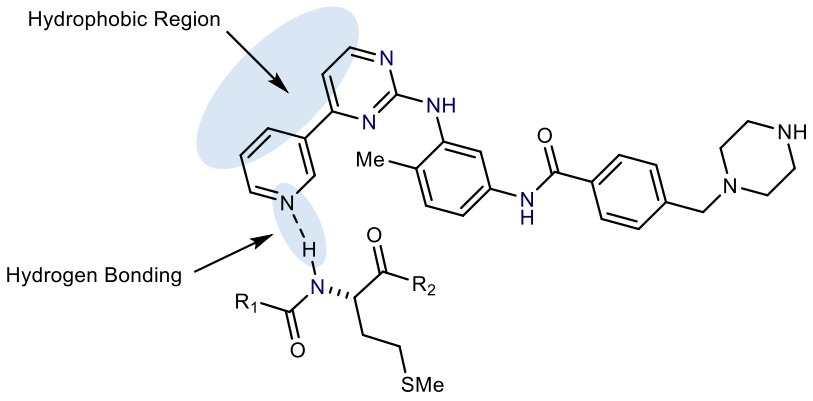


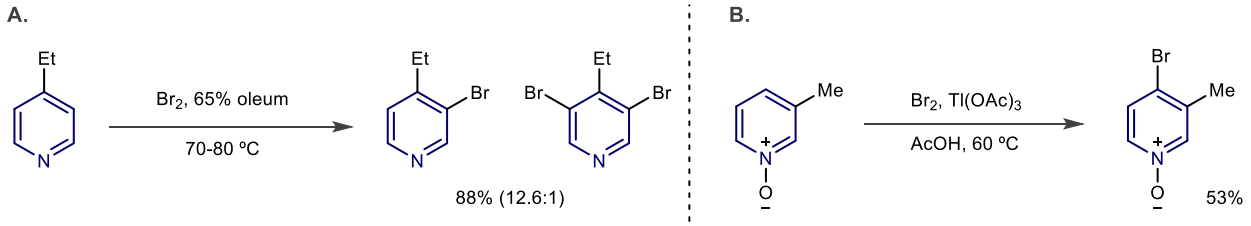
Figure 1.4: Hydrogen Bonding Between Gleevec and a Methionine Residue

1.4 Functionalization of Pyridine

1.4.1 Conventional Methods of Pyridine Functionalization

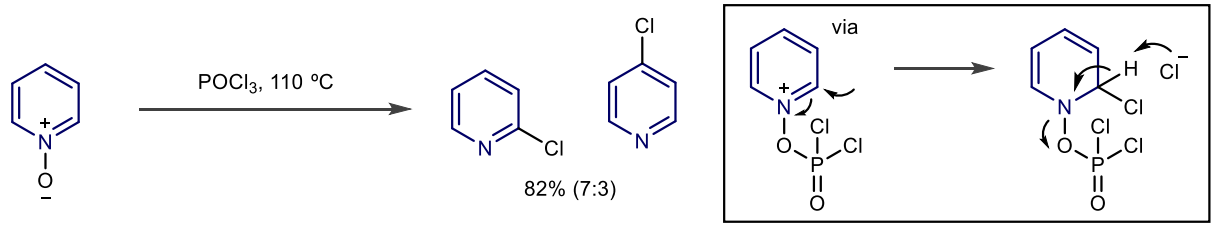
As pyridines are common in drug compounds, it is important to be able to synthesize new examples with a range of functional groups at different positions on the ring. A common approach to modify pyridine is through a versatile functional group such as a halogen. Halogens are commonly used in metal-catalysis and as precursors for radicals and anions. A halide can be installed on an aromatic by reacting it with an electrophilic halogen source via an electrophilic aromatic substitution (EAS) reaction. Halogenation via EAS on electron-rich arenes can be carried out at room temperature but for pyridine this process is extremely difficult given the π–deficient ring and thus requires harsher conditions.[6] For example, the bromination of pyridine requires heating in elemental bromine and sulfuric acid at elevated temperatures (**Scheme 1.1, A**).[14] These conditions are not applicable on pyridines with acid sensitive functionality or with groups which can preferential react with bromine. While 3-bromopyridne is the major product, dibromination can also occur. To increase the electron density in the ring, the N-oxide can be formed using an oxidant such as peroxide.[15] The lone pairs of the oxygen can donate into the ring causing pyridine to react with bromine at the 4-position (**Scheme 1.1, B**).[6] The N-oxide is removed using a reductant

such as triphenylphosphine or dimethyl sulfide. The additional steps to install and then remove the N-oxide lessen the practicality of this route.



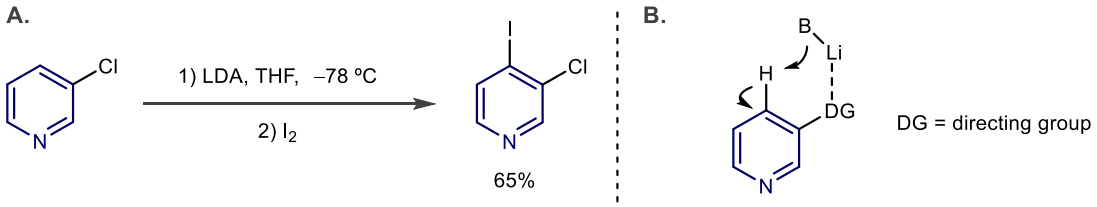
Scheme 1.1: Halogenation via EAS: A) 3-Bromination B) 4-Bromination via N-Oxides

Chlorination on pyridine N-oxides is carried out using phosphoryl chloride (**Scheme 1.2**).[16] The mechanism of this reaction involves the oxygen of the N-oxide attacking the phosphorus of the phosphoryl chloride releasing a chloride anion which then attacks either the 2- or 4-position of the pyridine. Subsequent base elimination provides the chloropyridine. Thionyl chloride has also been used in a similar manner as a chlorinating agent.[17]



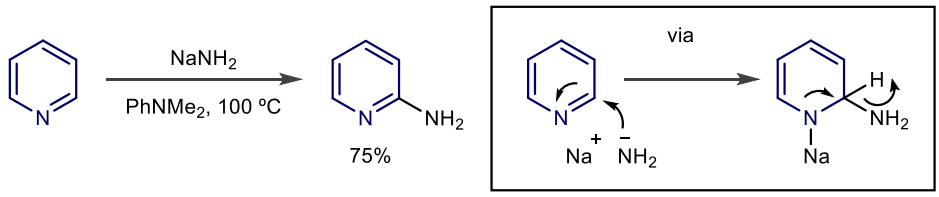
Scheme 1.2: Chlorination of Pyridine N-oxide

Direct metalation using strong bases followed by trapping with an electrophile is a common approach to install a halogen or to make a C–C bond on the pyridine ring.[18] Common bases for this process include alkyl lithiums and lithium amides. For substituted pyridines, selectivity is typically controlled using directing groups which can coordinate with the lithium ion. Depending on the substrate and conditions a pyridine can be selectively deprotonated (**Scheme 1.3**).[19,20]



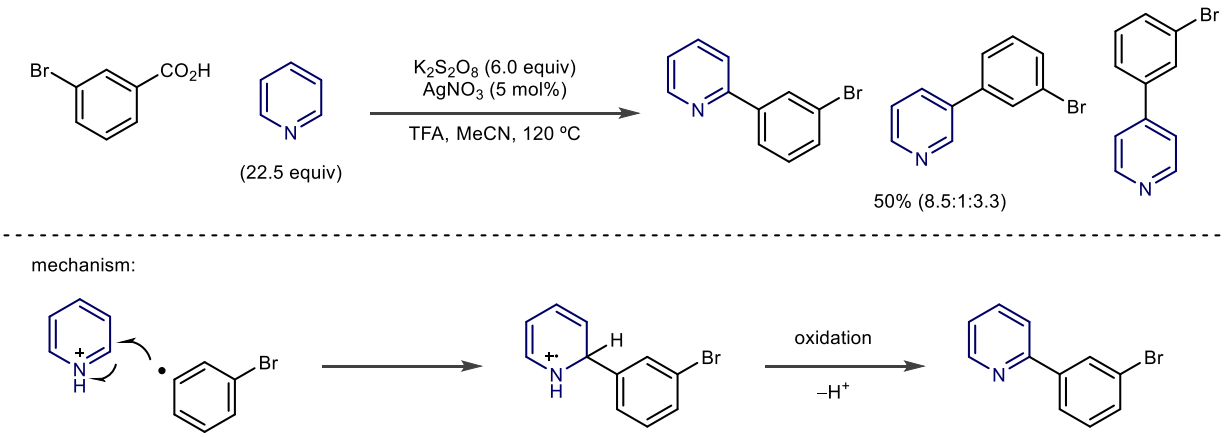
Scheme 1.3: Examples of Direct Metalation Followed by Trapping with an Electrophile

One of the oldest methods to functionalize pyridine is the Chichibabin reaction (**Scheme 1.4**). First disclosed in 1914, this method enables the 2-position amination of pyridine from sodium amide.[21] The mechanism of this reaction involves an addition-elimination where sodium amide attacks into the ring resulting in a Meisenheimer intermediate, which then subsequently loses hydride to regain aromaticity. Amination is a useful transformation as the 2-aminopyridine motif is present in various drug compounds such as Sonidegib[22] and Netupitant.[23]



Scheme 1.4: Example of the Chichibabin Reaction

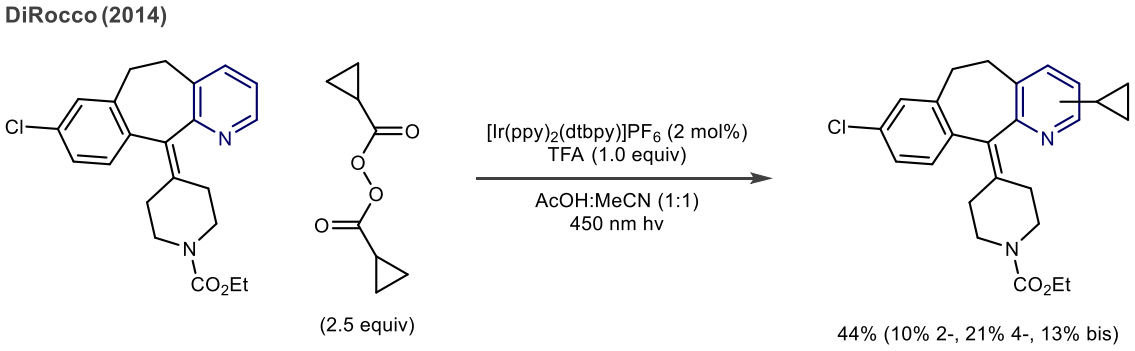
Pyridines are known to react with radicals via the Minisci reaction (**Scheme 1.5**).[24] In this process, a radical, typically an alkyl or aryl, is generated from a carboxylic acid precursor. The radical will add into the ring of a protonated pyridine forming a radical cation.[25] Abstraction of the adjacent hydrogen atom regains aromaticity of functionalized pyridine. The radical will selectively add to the most electrophilic position, which is the 2-positon, but will also react at the 3- and 4-positions.



Scheme 1.5: Example of the Minisci Reaction

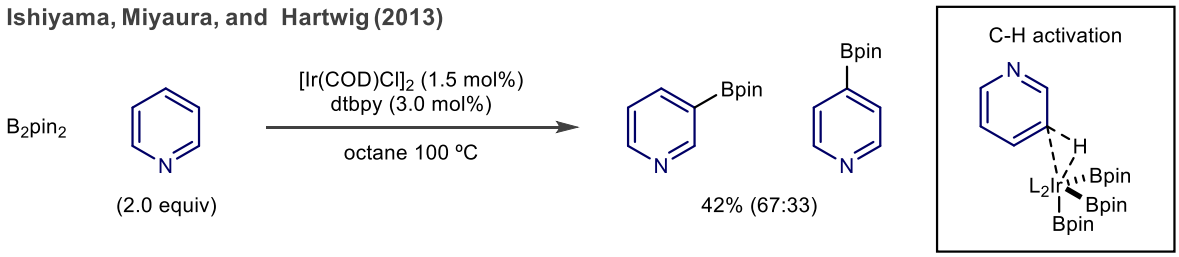
1.4.2 New Approaches to Functionalize Pyridine

A recent trend in pyridine functionalization is the incorporation of photocatalysis into the Minisci reaction. By using photocatalysis one circumvents the need for strong chemical oxidants and higher temperatures to generate the required radical.[26] The Merck process group took this approach when developing a mild set of conditions for the late-stage alkylation of pharmaceuticals. An iridium photocatalyst and blue light (450 nm) cause a peroxide precursor to decompose releasing an alkyl radical at room temperature. The alkyl radical then reacts with the protonated azine via a Minisci reaction. An example of this process applied to loratadine can be seen in **Scheme 1.6**. Other examples utilizing photoredox chemistry includes the important work from the Molander,[27] MacMillan,[28,29] and Stephenson[30] groups.



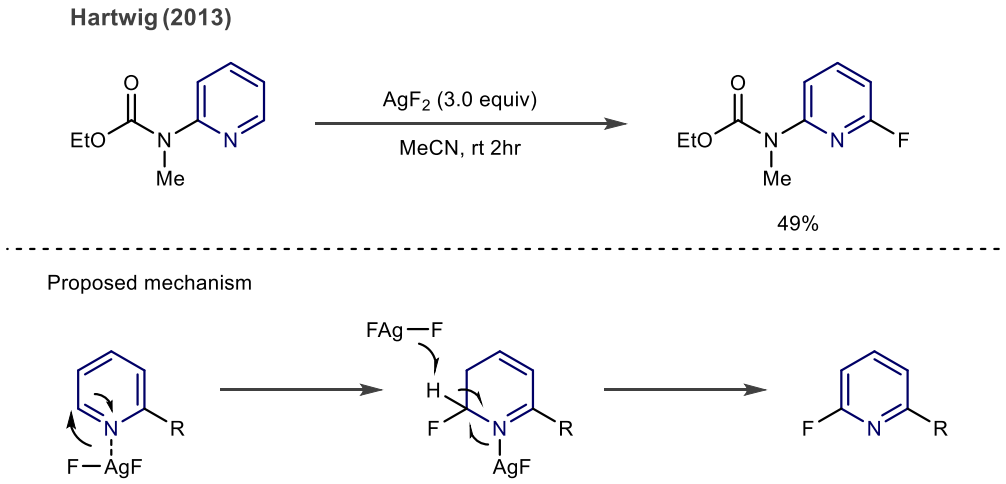
Scheme 1.6: Late-Stage Functionalization of Pharmaceuticals

The use of C–H activation has been a recent development in pyridine functionalization. One of the most commonly used methods is iridium-catalyzed borylation developed by Ishiyama, Miyaura, and Hartwig (**Scheme 1.7**).[31,32] The Ir(I) complex reacts with B_2pin_2 and the bipyridine ligand to form the active Ir(III) catalyst. C–H activation followed by reductive elimination yields the C–B bond. The reaction on unsubstituted pyridine gives a mixture of 3- and 4-borylated products with a 2:1 ratio, respectively. On substituted pyridines, the regioselectivity is largely influenced by sterics. The Bpin group is a versatile functional handle and thus its installation on pyridine is an important transformation. Jin Quan Yu's palladium-catalyzed C–H activation on pyridines should also be mentioned as an important finding in this area.[33]



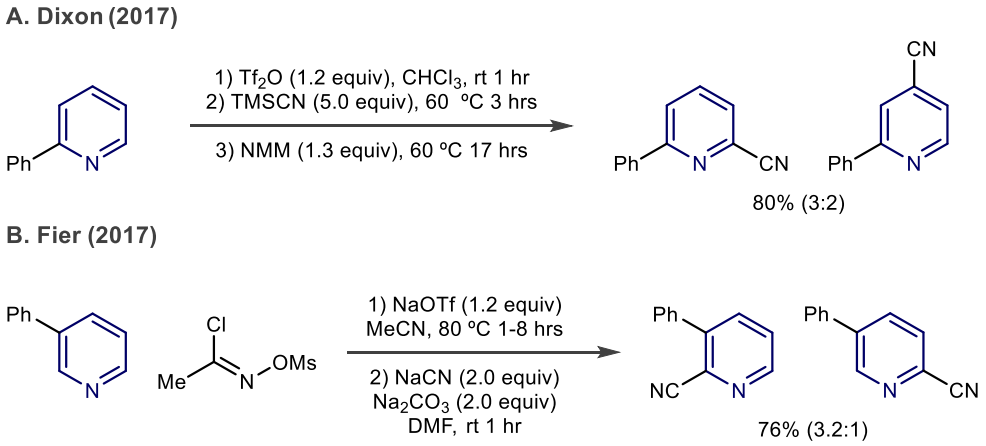
Scheme 1.7: Iridium Catalyzed Borylation of Pyridine

2-Fluoropyridines can easily be accessed by reacting a pyridine with silver(II) fluoride (AgF_2) in acetonitrile at room temperature. (**Scheme 1.8**).[34] This method, developed by the Hartwig group, installs a fluoro selectively at the 2-position of pyridine, and ortho to the nitrogen of other azines such as quinoline and diazines. 2-Fluoropyridnes are valuable precursors for S_NAr reactions providing easy access to C–O and C–N bonds when reacted with alcohols and amines, respectively. The mechanism of fluorination is believed to first involve the coordination of AgF_2 to the pyridine followed by the addition of one the fluorides to the 2-position. The abstraction of the ipso hydrogen by a second equivalent of AgF_2 yields the fluorinated product.



Scheme 1.8: Hartwig's 2-Fluorination of Pyridine

The 2-position cyanation of pyridine can be accomplished using an activating group such as a triflyl or oxime.[35,36] Addition of a cyanide anion into the pyridine ring followed by a base elimination of the activating group yields the 2-cyano product. Examples of these processes can be seen in **Scheme 1.9**.

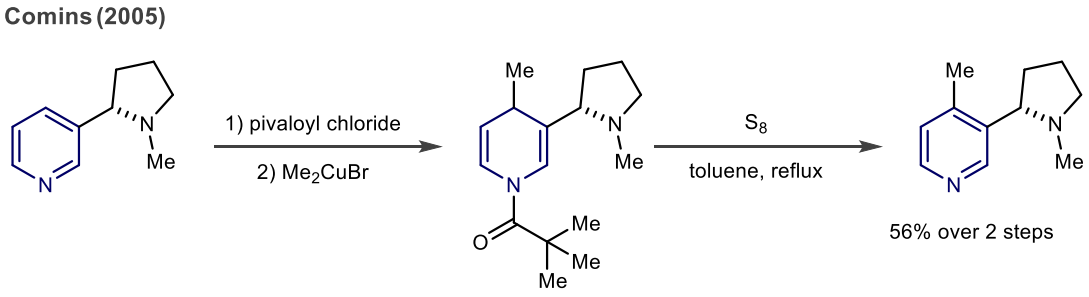


Scheme 1.9: Cyanation of Pyridine: A) Trifyl Activation B) Oxime Activation

1.4.3 4-Selective Methods

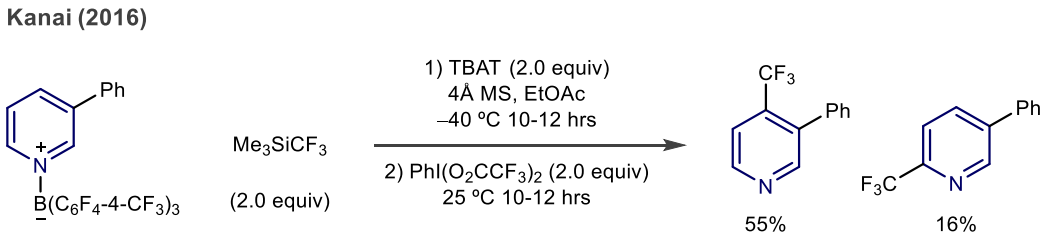
When compared with the 2- and 3-positions, methods to selectively functionalize the 4-position of pyridine are relatively scarce. One approach to selectively access the 4-position is to react the pyridine nitrogen with an electrophile to form a pyridinium which makes the ring more

electrophilic. Addition of a carbon nucleophile followed by an oxidant can introduce a C–C bond on the ring. The use of acyl pyridiniums in this application has been extensively studied by Daniel Comins and an example of this process can be seen in **Scheme 1.10** showing the 4-functionalization of nicotine.[37] Nicotine is first reacted with pivaloyl chloride to activate the pyridine. A Grignard is reacted with copper(I) bromide to form a cuprate which adds selectively to the 4-position to form an N-pivaloyl-1,4-dihydronicotine. Subjecting this dearomatized species to elemental sulfur in toluene at reflux forms the 4-functionalized product.



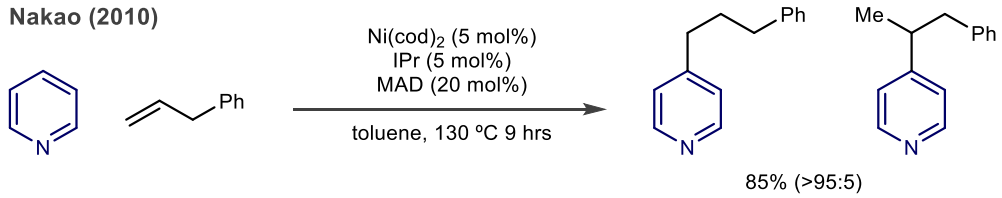
Scheme 1.10: Comins' 4-Functionalization of Nicotine

A similar approach was developed by the Kanai group to install perfluoroalkyl and perfluoroaryl groups to the 4-position of pyridine as well as other azines (**Scheme 1.11**).[38] A bulky borane Lewis acid is used to form the more electrophilic pyridinium and also prevents nucleophilic attack at the 2-positon due to its steric influence. Tetrabutylammonium difluorotriphenylsilicate (TBAT) reacts with the silane to release a trifluoromethyl anion which then attacks the 4-position of the activated pyridine. The resulting dearomatized species is then oxidized using an iodonium salt. While the reaction is selective for the 4-position, the presence of groups at the 3-position led to significant amounts of the 2- and 6-positon regioisomers.



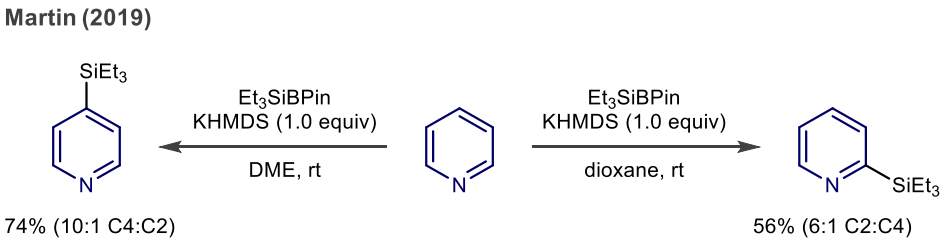
Scheme 1.11: Kanai's Trifluoromethylation of Pyridines and Azines

A bulky Lewis acid was also employed by the Nakao group in their 4-selective alkylation of pyridine (**Scheme 1.12**).[39] A bulky aluminum Lewis acid, methylaluminum bis (2, 6-di-t-butyl-4-methylphenoxide) (MAD), coordinates to the nitrogen of pyridine and then the nickel catalyst with an NHC ligand, IPr, undergoes oxidative addition into the para C–H bond. Migratory insertion across the alkene followed by reductive elimination yields the alkylated product with minor amounts of the secondary isomer.



Scheme 1.12: Nakao's 4-Selective Alkylation of Pyridine

In 2019, Rubin Martin developed a selective silylation of pyridine using $Et_3SiBPin$ and KHMDS (**Scheme 1.13**).[40] The silyl group has seen some interest due to its potential application in drugs, but can also be used as a functional handle for subsequent transformations. The reaction is believed to proceed by the formation of a distinct silyl anion which then attacks the pyridine ring. Interestingly, the selectivity can be controlled by solvent. When the solvent is dimethylethane (DME) the reaction favors the 4-position over the 2-position (10:1 for pyridine). When dioxane is used the selectivity switches to favor the 2-position (6:1). The process can be applied to pharmaceutical compounds as a way to do a late-stage silylation of azines.



Scheme 1.13: Selectivity of Silylation of Pyridine Controlled by Solvent

1.5 Conclusion

The functionalization of pyridine remains an important topic in synthesis given its relevance in pharmaceuticals. Despite being studied extensively, there remain deficiencies in this area. There are numerous methods to selectively functionalize the 2- and 3-positions of pyridine, but relatively few methods which target the para C–H bond. In subsequent chapters, the McNally group provides a solution to this problem by the selective installation of a phosphonium group to the 4-position of pyridine.

REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, 57, 10257.

(2) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, 9, 2265.

(3) Xie, J.; Luo, J.; Winn, T. R.; Cordes, D. B.; Li, G. *Beilstein J. Org. Chem.* **2014**, 10, 746.

(4) Ueda, S.; Su, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, 134, 700.

(5) Duan, S.; Place, D.; Perfect, H. H.; Ide, N. D.; Maloney, M.; Sutherland, K.; Wiglesworth, K. E. P.; Wang, K.; Olivier, M.; Kong, F.; et al. *Org. Process Res. Dev.* **2016**, 20, 1191.

(6) Joule, J. A.; Mills, K. *Heterocyclic Chemistry, 5th Ed*; Wiley/Blackwell Publishing Ltd, 2010.

(7) Terrier, F. *Modern Nucleophilic Aromatic Substitution*, 1st ed.; Wiley.

(8) Ishikawa, M.; Hashimoto, Y. *J. Med. Chem.* **2011**, 54, 1539.

(9) Patrick, G. L. *An Introduction to Medicinal Chemistry 5th Edition*; Oxford University Press.

(10) Cruciani, G.; Carosati, E.; De Boeck, B.; Ethirajulu, K.; Mackie, C.; Howe, T.; Vianello, R. *J. Med. Chem.* **2005**, 48, 6970.

(11) Bissantz, C.; Kuhn, B.; Stahl, M. *J. Med. Chem.* **2010**, 53, 5061.

(12) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, 57, 5845.

(13) Eck, M. J.; Manley, P. W. *Current Opinion in Cell Biologhy* **2009**, 21, 288.

(14) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1993**, 58, 271.

(15) Mosher, H. S.; Turner, L.; Carlsmith, A. **1953**, 33, 79.

(16) Yamanaka, H.; Araki, T.; Sakamoto, T. *Chem. Pharm. Bull.* **1988**, 36, 2244.

(17) Hwang, S. H.; Wecksler, A. T.; Zhang, G.; Morisseau, C.; Nguyen, L. V.; Fu, S. H.; Hammock, B. D. *Bioorg. Med. Chem. Lett.* **2013**, 23, 3732.

(18) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, 36, 1161.

(19) Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jorgensen, M. *Angew. Chem. Int. Ed.* **2008**, 47, 888.

(20) Rocca, P.; Marsais, F.; Godard, A.; Que´guiner, G. *Tetrahedron* **1993**, 49, 49.

(21) McGill, C.; Rappa, A. *Adv. Heterocycl. Chem.* **1988***,* 44, 1.

(22) Burness, C. B. *Drugs* **2015**, 75, 1559.

(23) Hoffmann, T.; Bös, M.; Stadler, H.; Schnider, P.; Hunkeler, W.; Godel, T.; Galley, G.; Ballard, T. M.; Higgins, G. A.; Poli, S. M.; et al. *Bioorg. Med. Chem. Lett.* **2006**, 16, 1362.

(24) Kan, J.; Huang, S.; Lin, J.; Zhang, M.; Su, W. *Angew. Chem. Int. Ed.* **2014**, 53, 2199.

(25) Duncton, M. A. J. *Med. Chem. Commun.* **2011**, 2, 1135.

(26) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. *Angew. Chem. Int. Ed.* **2014**, 53, 4802.

(27) Matsui, J. K.; Primer, D. N.; Molander, G. A. *Chem. Sci.* **2017**, 8, 3512.

(28) Jin, J.; MacMillan, D. W. C. *Nature* **2015**, 525, 87.

(29) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, 480, 224.

(30) Sun, A. C.; McAtee, R. C.; McClain, E. J.; Stephenson, C. R. J. **2019**, 51, 1063.

(31) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, 43, 5649.

(32) Sadler, S. A.; Tajuddin, H.; Mkhalid, I. A. I.; Batsanov, A. S.; Albesa-Jove, D.; Cheung, M. S.; Maxwell, A. C.; Shukla, L.; Roberts, B.; Blakemore, D. C.; et al. *Org. Biomol. Chem.* **2014**, 12, 7318.

(33) Ye, M.; Gao, G.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, 133, 6964.

(34) Fier, P. S.; Hartwig, J. F. *Science* **2013**, 342, 956.

(35) Fier, P. S. *J. Am. Chem. Soc.* **2017**, 139, 9499.

(36) Elbert, B. L.; Farley, A. J. M.; Gorman, T. W.; Johnson, T. C.; Genicot, C.; Lallemand, B.; Pasau, P.; Flasz, J.; Castro, J. L.; MacCoss, M.; et al. *Chem. Eur. J.* **2017**, 23, 14733.

(37) Comins, D. L.; King, L. S.; Smith, E. D.; Fe´vrier, F. C. *Org. Lett.* **2005**, 7, 5059.

(38) Nagase, M.; Kuninobu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2016**, 138, 6103.

(39) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, 132, 13666.

(40) Gu, Y.; Shen, Y.; Zarate, C.; Martin, R. *J. Am. Chem. Soc.* **2019**, 141, 127.

CHAPTER TWO

Heteroaryl Ether Synthesis using Heterocyclic Phosphonium Salts

2.1 Chapter Overview

The development of a new strategy to synthesize heteroaryl ethers is presented in this chapter. The heteroaryl ether motif is common in pharmaceuticals but is difficult to construct without prefunctionalized starting material, such as heteroaryl halides. As shown in section **1.4.1**, pyridines are difficult to halogenate beyond simple examples, thus more complex heteroaryl ethers cannot easily be accessed. Our two-step approach circumvents this requirement, allowing C–O bond formation from the C–H bond of a pyridine or diazine. Regioselective formation of a heterocyclic phosphonium salt followed by a reaction with an alkoxide yields the heteroaryl ether. This strategy was applied to a variety of pyridines ranging in complexity from building blocks to pharmaceuticals. My co-worker, Ryan Dolewski, developed the reaction to make the heterocyclic phosphonium salts and prepared most of the examples that would be used in this process. Professor Robert Paton carried out the computational analysis to help us understand the mechanism. Work presented in this chapter lead to a publication in the Journal of American Chemical Society[1] and subsequent publications using a similar approach.[2,3]

2.2 Background

2.2.1 Heteroaryl Ethers in Pharmaceuticals

A heteroaryl ether is a heteroaromatic featuring an ether linkage. This motif is common in pharmaceuticals with numerous examples featuring an azine, specifically. (**Figure 2.1**).

Sulfadoxine, a malaria treatment, and Bedaquline, a tuberculosis drug, are on the World's Health Organization's list of essential medicines and both contain the heteroaryl ether motif.[4] Two additional examples include Simeprevir and Grazoprevir which are treatments for hepatitis C.[5] Nexium, one of the top-selling drugs in 2012, has an ether linkage at the 4-position of the pyridine ring (**Figure 1.2**).[6] Other proton pump inhibitors such as Prevacid and Protonix are structurally similar to Nexium, having this heteroaryl ether motif.[7]

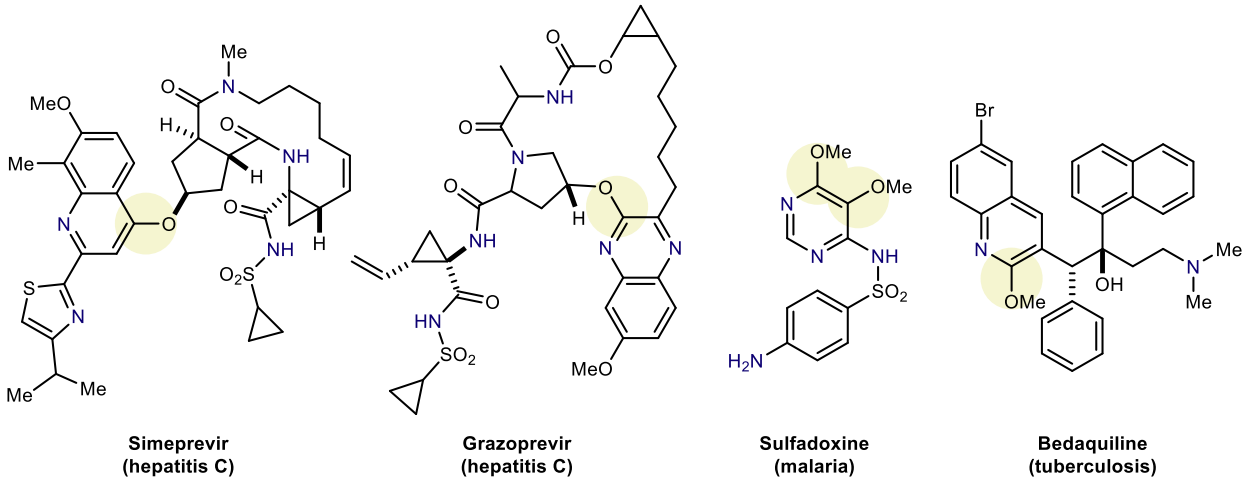
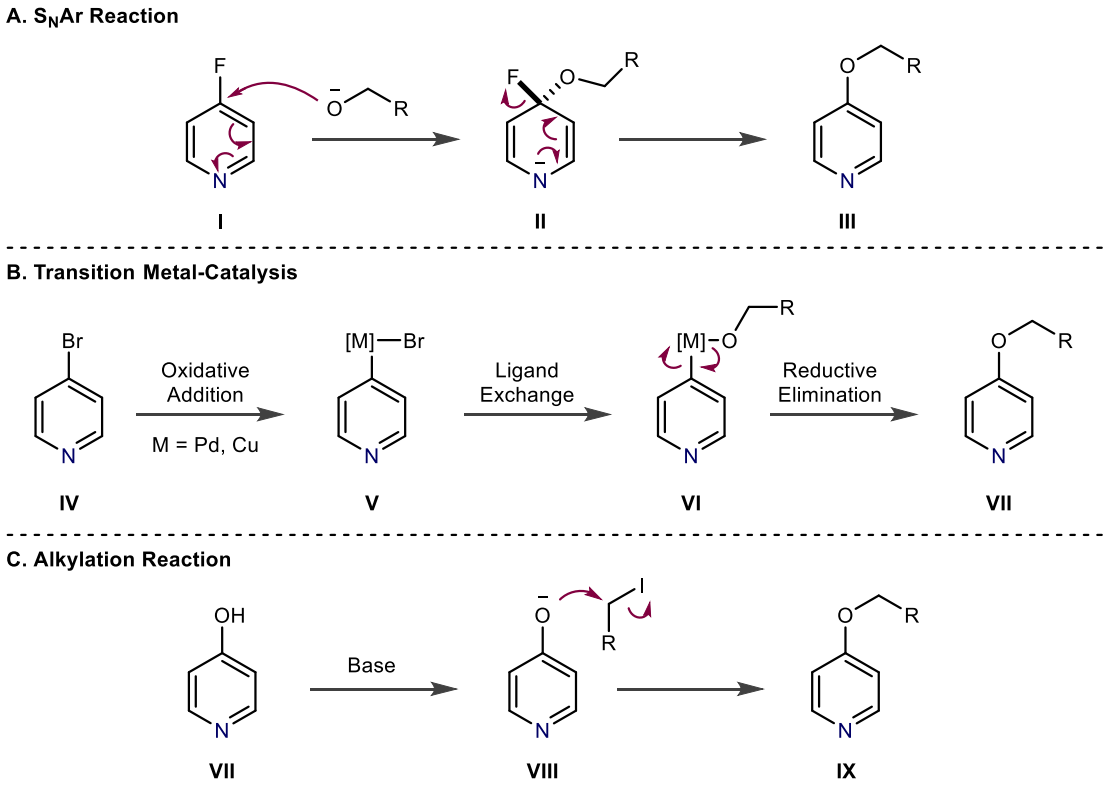


Figure 2.1: Heteroaryl Ethers Found in Pharmaceuticals

2.2.2 Conventional Methods to Prepare Heteroaryl Ethers

Heteroaryl ethers are typically prepared from heteroaryl halide and alcohol precursors.[8] Pyridines with a halogen or pseudo-halogen at the 2- or 4-position can react with alcohols or alkoxides via a nucleophilic aromatic substitution (S_NAr) process (**Scheme 2.1, A**).[9] Reactions at the 3-position of pyridine are generally more difficult often requiring additional withdrawing groups on the ring or high temperatures. The S_NAr reaction begins with the nucleophilic attack of the alkoxide on the *ipso* position of a leaving group (**I**) resulting in a charged intermediate known as a Meisenheimer complex (**II**). Elimination of the leaving group yields the rearomatized product

with an ether linkage (**III**). More recent studies show that the S_NAr reaction on pyridine could also be concerted, forgoing a charged intermediate.[10] The rate-determining step of a S_NAr reaction is the attack of the nucleophile on the pyridine ring. Since electron-deficient rings have faster reaction rates, pyridines with electron-withdrawing groups such as fluoro, chloro, and nitro groups are typically used. In examples featuring more than one halide at an S_NAr active position, such as 2,4-dichloropyidine, there may be a lack of regiocontrol depending on the nucleophile and the conditions.[11]



Scheme 2.1: Conventional Methods to Synthesize Heteroaryl Ethers: A) S_NAr Reactions B) Metal-Catalysis C) Alkylation reactions

Heteroaryl ethers are also prepared using transition metal-catalysis (**Scheme 2.1, B**).[12–15] A metal catalyst, typically palladium or copper, oxidatively inserts into the carbon-halogen bond (**V**). Next there is a ligand exchange at the metal center between an alcohol or alkoxide and the

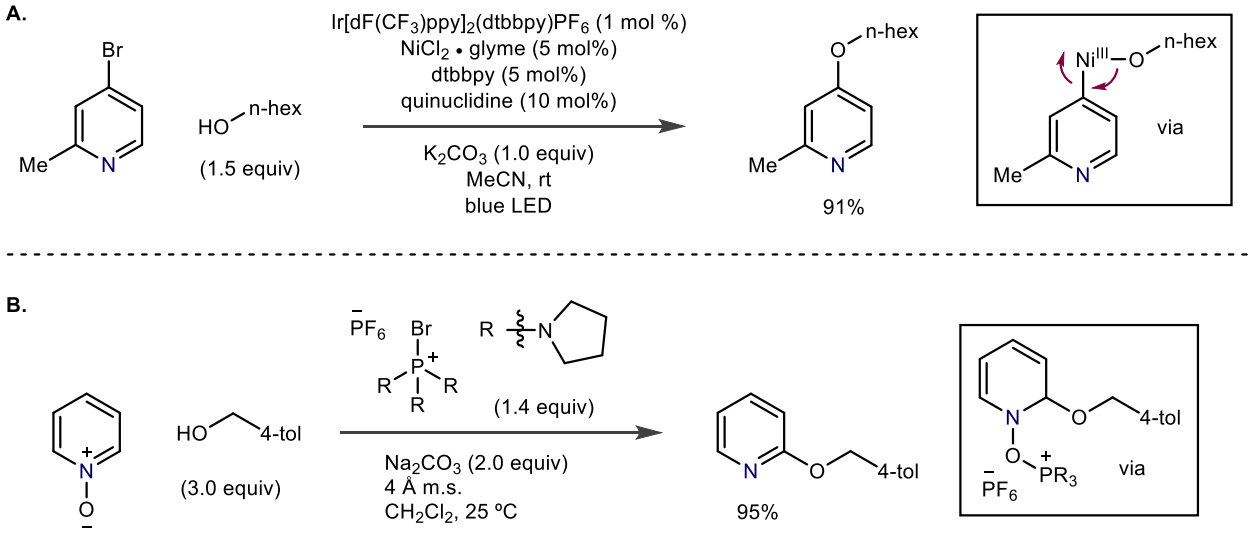
halide (**VI**). Reductive elimination forms the C–O bond (**III**) while reducing the metal and regenerating the catalyst.

Alkylation is another approach to construct heteroaryl ethers but requires the preinstalled hydroxyl functionality (**Scheme 2.1, C**).[16] In this process, a base is used to deprotonate the hydroxyl group (**VIII**) which is then alkylated using an alkyl halide via an S_N2 mechanism (**IX**). Competing reactivity at the nitrogen atom complicates this process.

2.2.3 Recent Methods to Prepare Heteroaryl Ethers

A novel method from MacMillan uses nickel catalysis in combination with photochemistry to construct C–O bonds (**Scheme 2.2, A**).[17] Like previous methods using metal-catalysis, this requires a heteroaryl halide and an alcohol, but in this case, nickel is used instead of palladium or copper. Nickel is generally not used as a catalyst in heteroaryl ether formation because the resulting nickel(II) aryl alkoxide complex will not easily undergo reductive elimination. Using photocatalysis, the Ni(II) complex can be oxidized to a more reactive Ni(III) species making reductive elimination more facile.

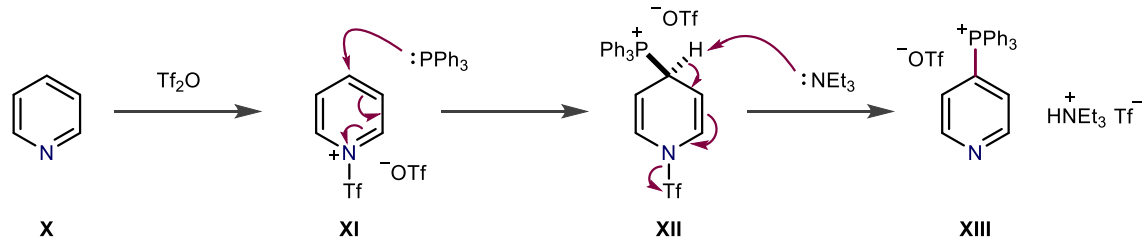
A medicinal chemistry group from Pfizer developed a straightforward approach to install a heteroaryl ether linkage at the 2-position of a pyridine from the corresponding *N*-oxide (**Scheme 2.2, B**).[18] Using a phosphonium activating group known as PyBroP, this reaction is carried out under mild conditions. The oxygen of the pyridine *N*-oxide attacks PyBroP displacing a bromide. The resulting activated complex is then attacked at the 2-position of pyridine by an alcohol, and elimination of the phosphoramide provides the heteroaryl ether.



Scheme 2.2: Recent Examples of Heteroaryl Ether Synthesis: A) MacMillan's Aryl Ether Synthesis using Photoredox Catalysis B) Pfizer's Heteroaryl Ether Synthesis from N-oxides

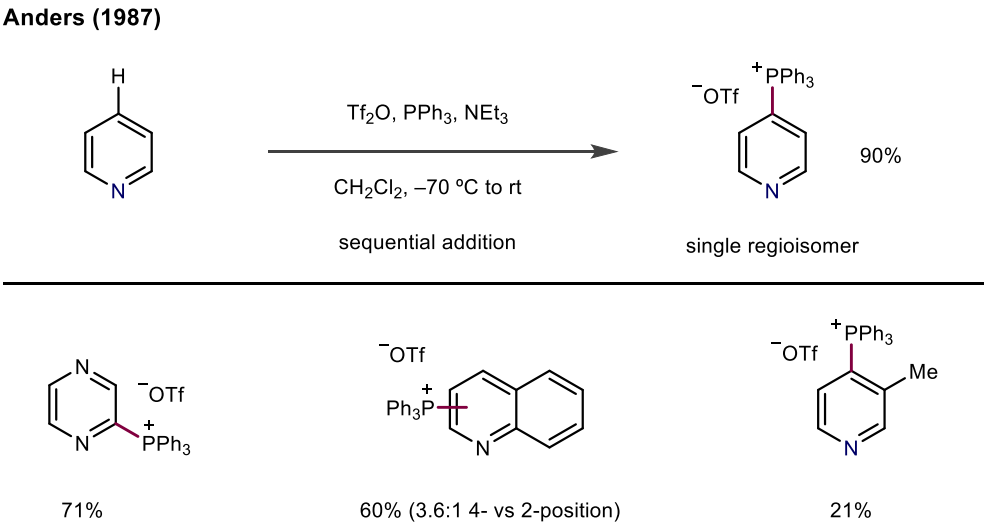
2.2.4 Anders' Initial Findings on Heterocyclic Phosphonium Salts

A seminal report from Ernst Anders provided a framework for the synthesis of heterocyclic phosphonium salts (**Scheme 2.3**).[19] Pyridine (**X**) was reacted with triflic anhydride (Tf_2O) at low temperatures in dichloromethane to form a triflyl pyridinium salt **(XI**). Addition of triphenylphosphine into the ring results in a dearomatized intermediate (**XII).** Triethylamine (NEt_3) enables elimination of the triflyl group to regain aromaticity and form the phosphonium salt (**XIII**). The triflyl ammonium byproduct is removed in a water workup.



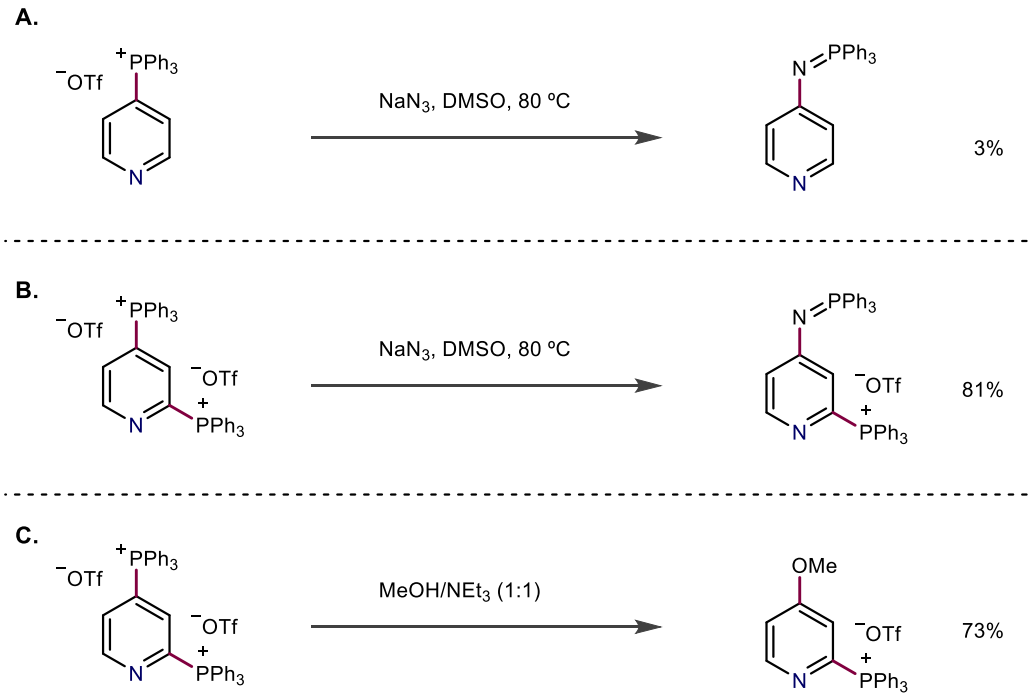
Scheme 2.3: Mechanism of Heterocyclic Phosphonium Salt Formation

One of the most important aspects of this reaction was its regioselectivity. The phosphonium group was installed with complete selectivity at the 4-position of pyridine (Scheme **2.4**). When applied to pyrazine this method worked reasonably well, with a yield of 71%. For quinoline, the selectivity worsens with 47% of the 4-position isomer versus 13% of the 2-position. A large deficiency in this method was its application on 3- and 5-substituted pyridines. 3-Methylpyidine, for example, gave a low yield of 21%.



Scheme 2.4: Anders' Method of Phosphonium Salt Formation

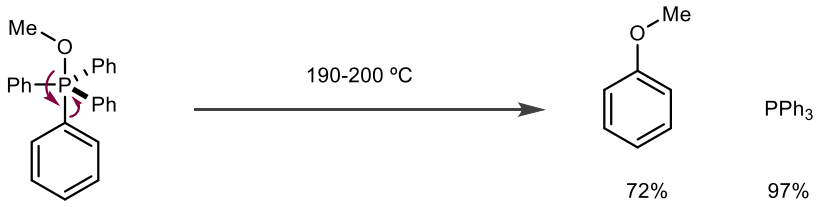
The reactivity of the heterocyclic phosphonium salts was explored by Anders although most of this work focused on transformations from the bis-phosphonium salt. These salts featuring a second phosphonium group are inherently more reactive, but the additional step to synthesize them make them significantly less practical. Sodium azide could be reacted with 4-pyridyl phosphonium salt to form an iminophosphorane in 3% yield (**Scheme 2.5, A**), however, when the bis-salt was used, the yield increases to 81% (**Scheme 2.5, B**).[19] A heteroaryl ether could also be formed in 73% yield by reacting the bis-salt with methanol and triethylamine (**Scheme 2.5, C**).[20]



Scheme 2.5: Initial Examination of Reactivity by Anders: A) Iminophosphorane from the Phosphonium Salt, B) Iminophosphorane from the Bis-Phosphonium Salt C) Methoxylation from the Bis-Phosphonium Salt

2.2.5 C–O Bond Construction via Phosphorus Ligand-Coupling

Aryl ethers could be formed from a phosphorane through a process known as ligand-coupling. By heating methoxy-tetraphenylphosphorane to 190-200 °C, anisole and triphenylphosphine can be produced (**Scheme 2.6**).[21] It has been proposed that this transformation proceeds via a concerted mechanism where the C–O bond is formed while the C–P and C–O bonds are broken.[22] The hypervalent P(V) phosphorus is reduced to the lower P(III) oxidation state in this process. Findings presented later in this work suggest that a concerted mechanism is incorrect.

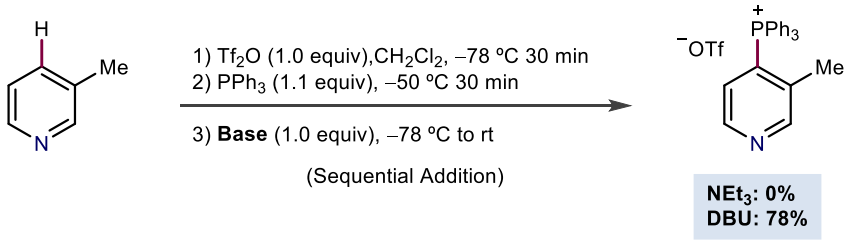


Scheme 2.6: C–O Bond Formation via Apical-Apical Ligand-Coupling

2.3. Results and Discussion

2.3.1 Improved Conditions to Make Heterocyclic Phosphoniums Salts

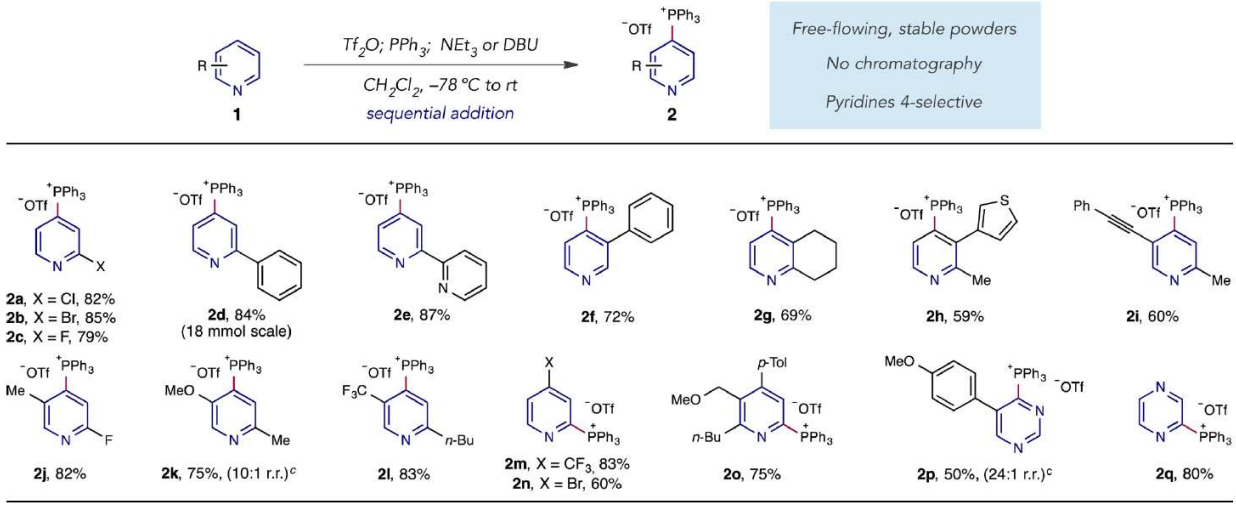
Since Anders' initial findings in the late 1980s, the heterocyclic phosphonium salts found no practical use in synthesis. Given the medicinal relevance of pyridines and the difficulty in functionalizing these structures regioselectivity, the McNally lab looked at using the phosphonium group as a functional handle to carry out subsequent transformations. To make this approach synthetically useful we had to expand the scope of the phosphonium salts. Ryan Dolewski, a co-worker in the McNally lab, was able to improve the generality of the reaction by changing the base. Use of triethylamine gave low to no yields when the pyridine had a substituent at the 3- or 5-position. It was found that 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) would give high yields on these same substrates. For example, when triethylamine is used as the base in making the phosphonium salt on 3-methylpyridine, it was found to give a 0% yield in our hands versus 21% that Anders reported. Triethylamine is believed to have failed because of a steric clash between its alkyl groups and the 3-methyl group on pyridine. When DBU is used, the yield increases to 78% (**Scheme 2.7**). With this finding, the scope of the reaction could be dramatically expanded.



Scheme 2.7: Importance of Base in the Phosphonium Salt Reaction

The reaction is compatible with a wide range of pyridines (**Table 2.1**) with complete selectivity for the 4-position in the large majority of examples.[1] The salts are typically free-flowing powders, benchtop stable, and only in a few rare cases did we observe decomposition over time. The purification of these compounds involves precipitation from diethyl ether, avoiding the need for column chromatography. Pyridines with a halogen at the 2- or 4-position (**2a-2c**, **2j**, and **2n**) undergo the reaction without concerns of halide displacement. The method can tolerate bulky substituents such as phenyl (**2f**) or trifluoromethyl groups (**2l**) at the 3- or 5-position despite a potential steric clash with triphenylphosphine. Examples of 2,3- (**2g** and **2h**), 2,5 (**2i**-**2l**), and 3,5-disubstituted[2,23] pyridines have all been shown to work well, and only in a few examples did we observe minor amounts of regioisomers (**2k** and **2p**). For 4-substituted pyridines, the phosphonium is instead installed at the 2-position (**2m**-**2o**), and diazines such as pyrazines (**2p**) and pyrimidines (**2q**) are also compatible. More complex structures such as the 2,3,4-trisubstituted example **2o** can also be formed in good yield.

Table 2.1: Conditions and Scope of Heterocyclic Phosphonium Salts

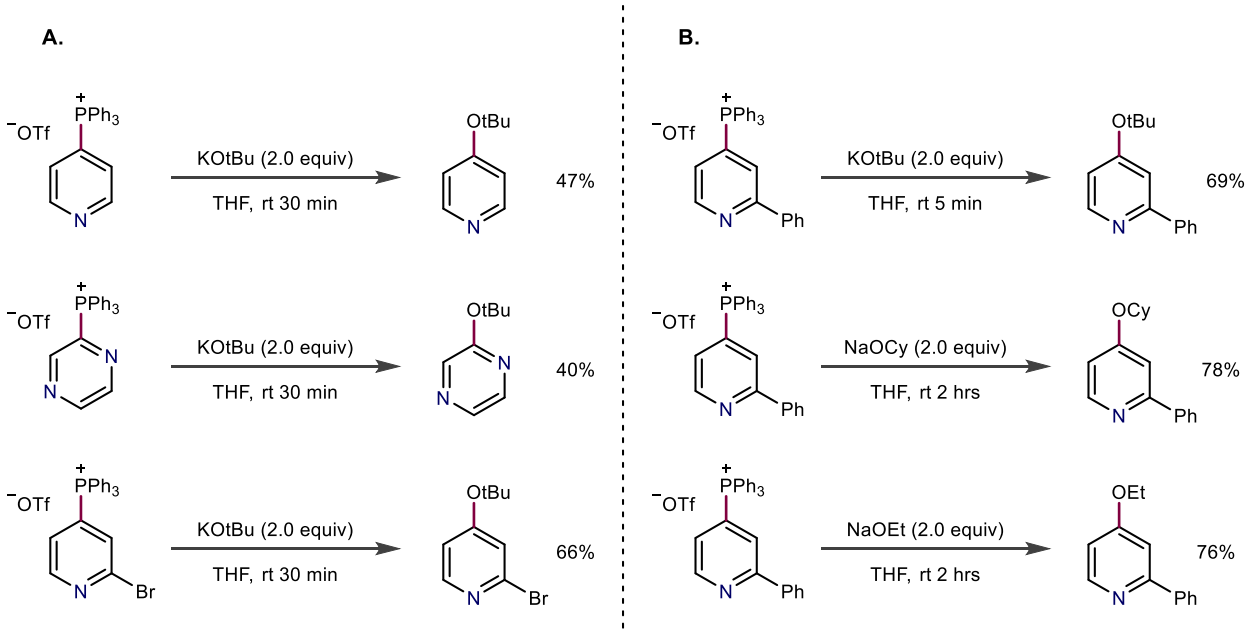


[a]Typical reaction stoichiometry: heteroaromatic (1.0 equiv), Tf_2O (1.0 equiv), PPh_3 (1.1 equiv), organic base (1.0 equiv). [b]Isolated yields of single regioisomers (unless stated) are shown. [c]r.r. = regiomeric ratio. For **2k** and **2p**, the minor product is the 2-phosphonium salt isomer and the crude ^1H NMR ratios are 10:1 and 20:1, respectively.

Reproduced with permission from *J. Am. Chem. Soc.* **2016**, *138*, 13806. Copyright 2016 American Chemical Society.

2.3.2 Development of a Heteroaryl Ether Synthesis using Phosphonium Salts

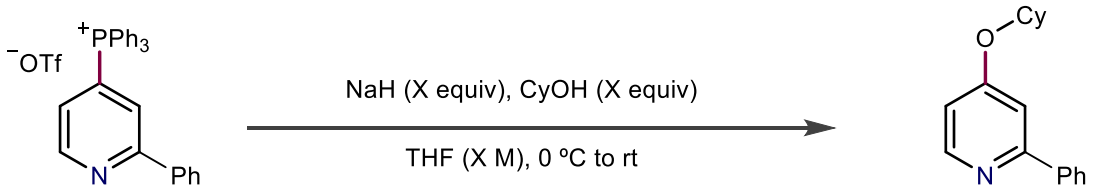
To install a carbon-heteroatom bond on pyridine, we proposed reacting the phosphonium salt with a nucleophile, such as an alkoxide, to displace triphenylphosphine via an S_NAr reaction. An initial successful result came when the phosphonium salt of pyridine was reacted with two equivalents of potassium tert-butoxide in tetrahydrofuran (THF) at room temperature to form 4-(tert-butoxy)pyridine in 47% yield after 30 minutes (**Scheme 2.8**). Phosphonium salts of pyrazine and 2-bromopyridine were subjected to the same conditions and both gave reasonable yields of the corresponding heteroaryl ether in 40% and 66%, respectively. Different alkoxides were reacted with the 2-phenylpyridine phosphonium salt and the primary, secondary, and tertiary examples all gave good yields ranging from 69% to 78%. Notably, potassium tert-butoxide consumed all the phosphonium salt after only 5 minutes. The sodium alkoxides were prepared by deprotonation of the corresponding alcohol with NaH. Other solvents were explored but THF proved to provide the best yields.



Scheme 2.8: Initial Survey of Reactivity A) Azine Phosphonium Scope B) Alcohol Scope

The reaction of the 2-phenylpyridine phosphonium salt (**2d**) with cyclohexanol and NaH was optimized by vary the conditions (**Table 2.2**). The amount of alkoxide (**entry 1-3**) had a small influence with 1.5 equivalents giving the highest yields. Excess alcohol or NaH did not improve the yield (**entry 4** and **5**), while concentration was found to be the most important factor as can be seen in **entries 6-8**. Diluting the reaction from 0.25 M to 0.125 M lowered the yield while increasing the concentration to 0.5 M and 1.0 M gave the highest amount of product formation.

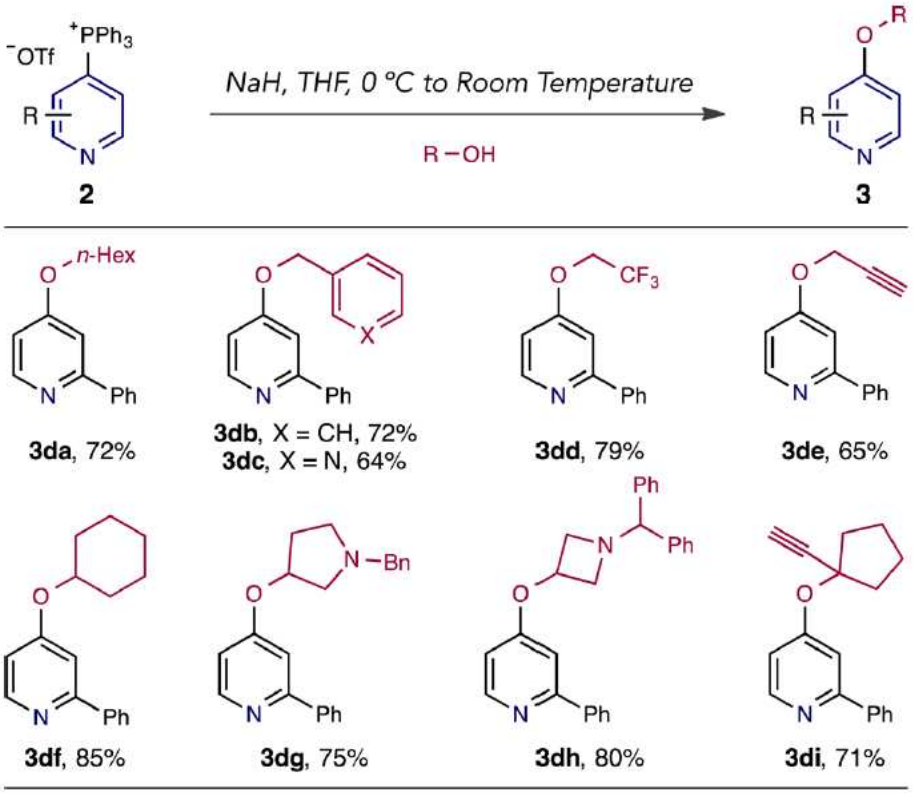
Table 2.2. Optimization of Reaction Conditions for Heteroaryl Ether Synthesis



Entry	NaH (equiv)	CyOH (equiv)	Concentration (M)	% Product
1	1.0	1.0	0.25	76
2	1.5	1.5	0.25	81
3	3.0	3.0	0.25	70
4	1.0	1.5	0.25	76
5	3.0	1.5	0.25	70
6	1.5	1.5	0.125	61
7	**1.5**	**1.5**	**0.5**	**89**
8	1.5	1.5	1.0	89

We next examined the scope of alcohols compatible in this reaction (**Table 2.3**). Primary, secondary, and tertiary alcohols all work well despite the potential steric clash of the bulkier alkoxides. Use of benzyl alcohol yields **3db** which can be hydrogenated to introduce hydroxyl functionality. Metal hydroxides have been shown to decompose the salts and thus a direct hydroxylation is not applicable. Despite reduced nucleophilicity, trifluoroethanol (**3dd**) can be used to form the corresponding heteroaryl ether in high yield. Propargyl alcohol (**3de**) allows for installation of an alkyne for potential application in click chemistry. Alcohols featuring other heterocycles (**3dc, 3dg,** and **3dh**) work without issue.

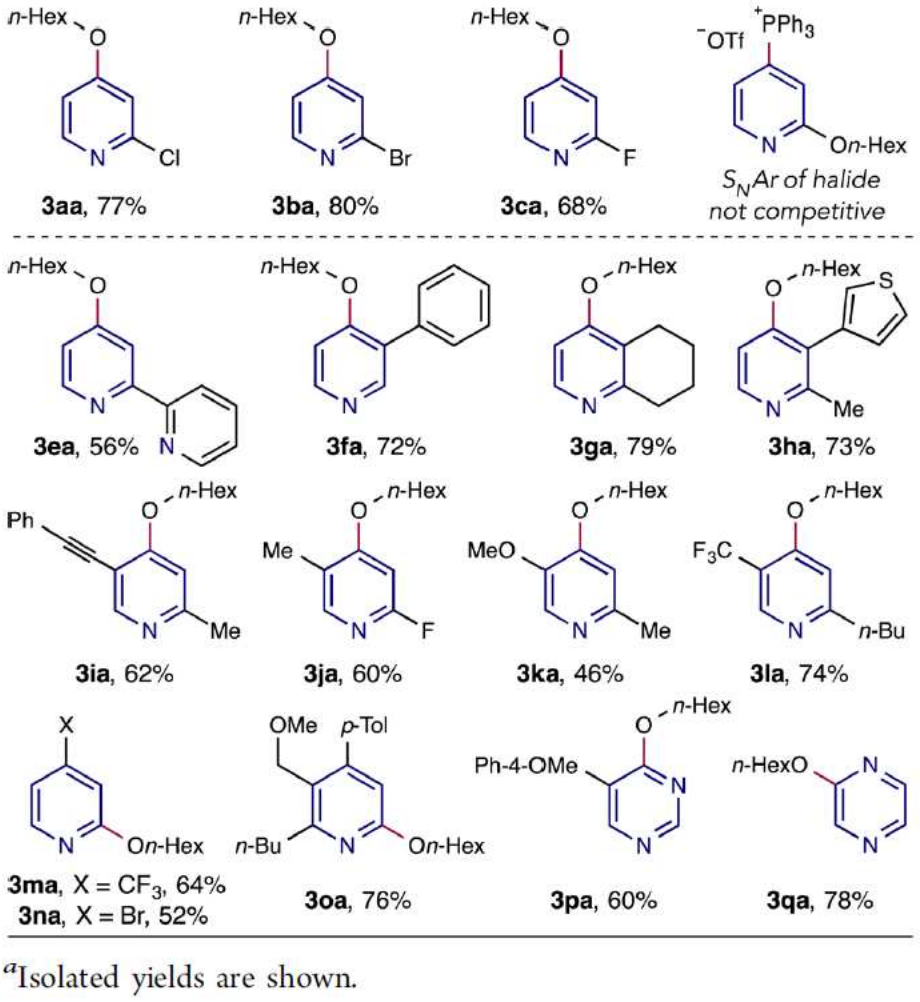
Table 2.3: Conditions and Scope of Heteroaryl Ethers using Different Alcohols



Reproduced with permission from *J. Am. Chem. Soc.* **2016**, *138,* 13806. Copyright 2016 American Chemical Society.

The scope of the heterocyclic phosphonium salts was then examined using sodium hexan-1-olate as our nucleophile (**Table 2.4**).[1] The reaction is chemoselective over halogens at the 2-position of pyridine. Phosphonium salts of 2-chloro (**3aa**) and 2-bromopyridine (**3ba**) showed only trace halide displacement. Examples with a 2-fluoro group (**3ca and 3ja**) gave only minor amounts (<10%) of the undesired product from S_NAr processes. Bulky substituents **(3fa** and **3ha**) at the 3- or 5-positions do not impede attack of the alkoxide. Pyridines featuring donating (**3ka**) or withdrawing groups (**3la**) work in reasonable yield despite changes in electronics on the ring, and pyrimidines (**3pa**) and pyrazines (**3qa**) are good substrates in this system.

Table 2.4: Conditions and Scope of Heteroaryl Ethers using Different Phosphonium Salts



[a]Isolated yields are shown.

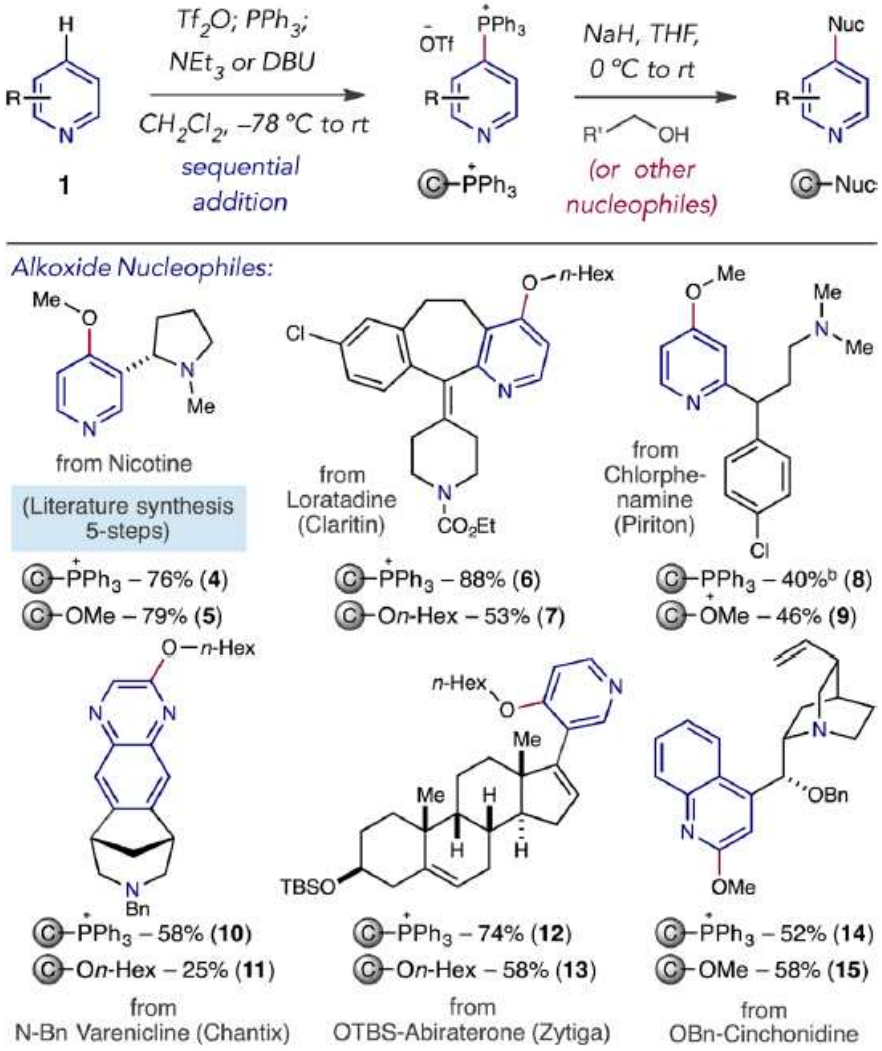
Reproduced with permission from *J. Am. Chem. Soc.* **2016**, *138,* 13806. Copyright 2016 American Chemical Society.

2.3.3 Late-Stage Functionalization of Pharmaceuticals and Bioactive Molecules

Late-stage functionalization is the introduction of new functionality on a complex substrate later in its synthesis.[24–26] This approach can significantly reduce the amount of work required to access derivatives by circumventing the need to design a different route for each new product. Late-stage functionalization can be applied to compounds which are already bioactive to potentially discovery a new drug. The phosphonium group can be installed on various pharmaceuticals which contain a pyridine and reacting these salts with an alkoxide provides an

easy route to install an ether linkage and thus accomplish late-stage functionalization (**Table 2.5**).[1] Nicotine worked well in this 2-step process despite the aliphatic amine within its structure (**4,5**). The methoxy derivative was found to take upwards to 5 steps from a literature synthesis.[27] The carbamate group in Loratadine did not interfere with salt (**6**) or heteroaryl ether formation (**7**). Installing the phosphonium on Chlorphenamine failed initially, which we suspected was due to the presence of the amine. To solve this problem one equivalent of triflic acid was added to protonate the amine. A protected version of Chantix could be used in this process but the salt formation on a quinoxaline requires higher temperatures. The reaction with the alkoxide was relatively low yielding for this substrate (**11**). The acyl group of the Zytiga phosphonium salt underwent transesterification when reacted with alkoxides. Converting the acyl to an OTBS group resolved this problem. The hydroxyl of Cinchonidine could be protected with a benzyl group enabling both steps of this process to work without issue.

Table 2.5: Late-Stage Functionalization of Pharmaceuticals and Bioactive Molecules



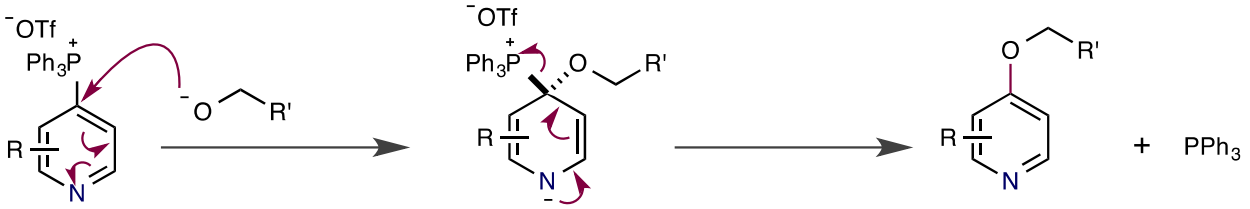
Reproduced with permission from *J. Am. Chem. Soc.* **2016**, *138,* 13806. Copyright 2016 American Chemical Society.

2.4 Mechanism

2.4.1 Proposed Mechanism of C–O Bond Formation

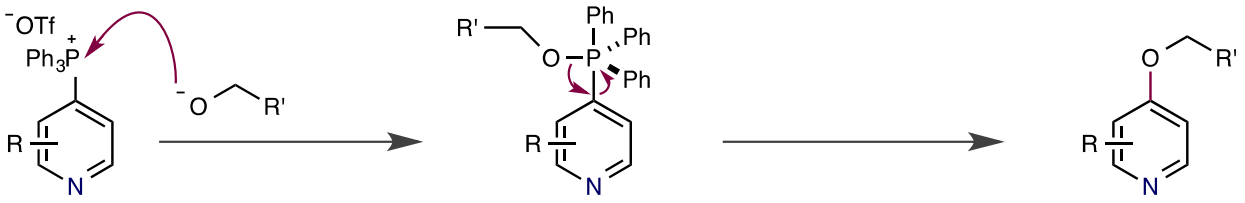
Heteroaryl ether formation from the phosphonium salt is thought to go through one of two different mechanisms. This transformation could be an S_NAr mechanism where the alkoxide nucleophile attacks the *ipso* position of the phosphonium salt.[8] By either a stepwise or concerted

process, triphenylphosphine is displaced providing the heteroaryl ether (**Scheme 2.9**).



Scheme 2.9: Heteroaryl Ether Formation via S_NAr

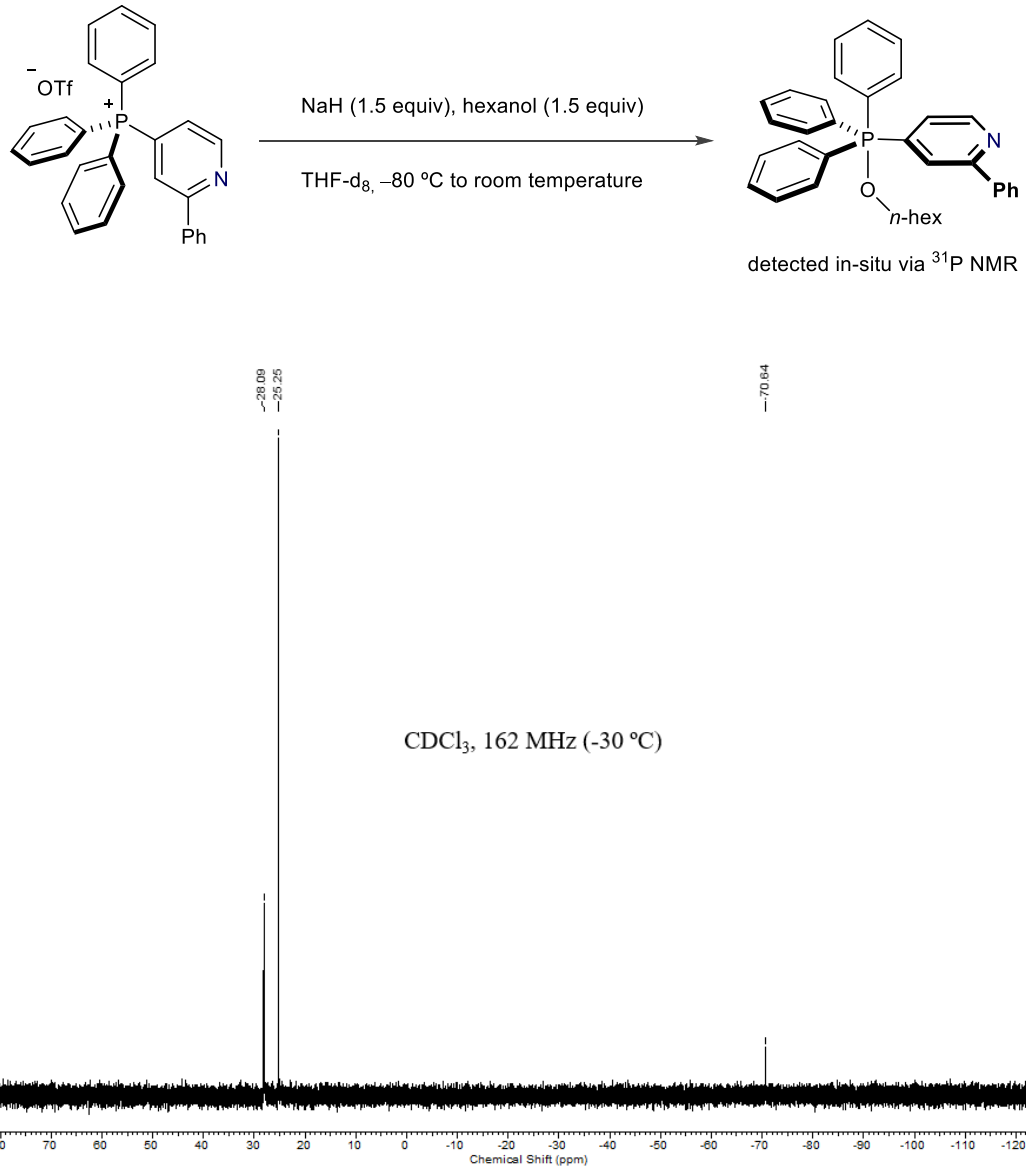
Another possible mechanism for heteroaryl ether formation is phosphorus ligand-coupling (**Scheme 2.10**). In this process, the alkoxide nucleophile directly attacks the phosphorus atom of the phosphonium salt, leading to a P(V) phosphorane. This intermediate can couple two of its ligands while reducing the phosphorus atom to a P(III) oxidation state.[22] This pathway yields the same products as the S_NAr process, a heteroaryl ether and triphenylphosphine.



Scheme 2.10: Heteroaryl Ether Formation via Phosphorus Ligand-Coupling

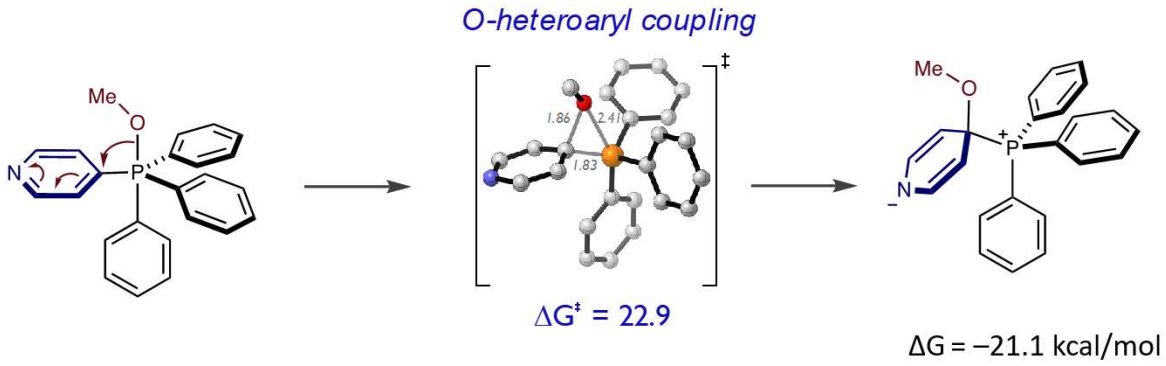
Unlike the S_NAr mechanism, ligand-coupling is relatively unexplored. To provide evidence of this pathway we attempted to observe the phosphorane intermediate in-situ via ^{31}P NMR analysis. We carried out the reaction between the 2-phenylpyridine salt and sodium hexan-1-olate at −80 °C in deuterated THF and progressively increased the temperature. Initially, only the resonances of the phosphonium (25.25 ppm) and triphenylphosphine oxide (28.09 ppm) were observed. The oxide was attributed to undesired side reactions when setting up the experiment. Once the reaction was warmed to −30 °C a new peak was observed at −70.64 ppm (**Scheme 2.11**).

This chemical shift falls in the range of a phosphorane species.[29] Warming to 0 °C and then to room temperature showed this peak growing in intensity. Detection of this intermediate provides evidence that this reaction was going through ligand-coupling. At room temperature, triphenylphosphine is detected as a byproduct of heteroaryl ether formation and after several hours the phosphorane peak disappears and the triphenylphosphine peak increases in size.



Scheme 2.11: Detection of Phosphorane Intermediate by in-situ ^{31}P NMR at –30 °C

A computational study from Professor Robert Paton provided additional evidence that this reaction is proceeding through a step-wise ligand-coupling mechanism. After phosphorane formation, the alkoxyl group occupying an apical position is thought to migrate onto the pyridine occupying one of the equatorial positions, leading to a dearomatized intermediate. This migration proceeds through a 3-center-4-electron bond between the phosphorus, *ipso* carbon of pyridine, and the oxygen of the alkoxyl group (**Scheme 2.12**). DFT calculations indicate that the energy barrier for this process is relatively low at 22.9 kcal/mol and the ΔG of the resulting dearomatized intermediate is –21.1 kcal/mol. Phenyl migration is a possible outcome, but the energy barrier is 7.4 kcal/mol higher and it is not observed experimentally. Elimination of triphenylphosphine gives the heteroaryl ether product.

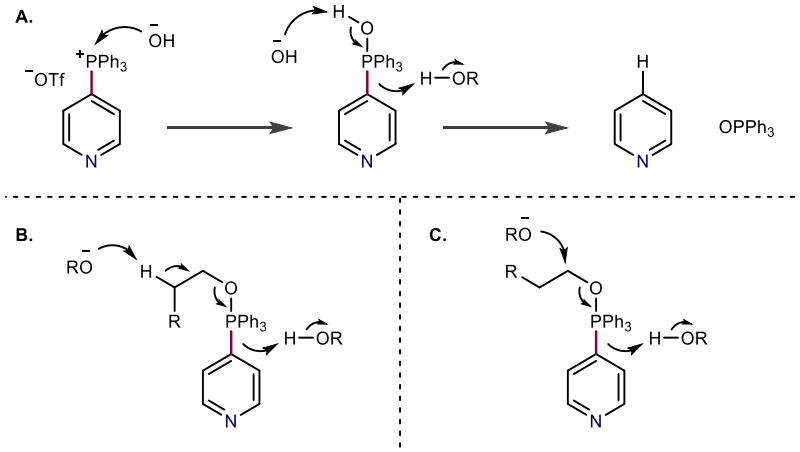


Scheme 2.12: DFT Calculated Transition State

2.4.2 Undesired Pathways

The reaction between the heterocyclic phosphonium salts and an alkoxide can lead to some undesired products such as triphenylphosphine oxide and the C–H product (the result of the phosphonium group being replaced with a hydrogen atom). One possible explanation for these compounds is the presence of hydroxide from water contamination. Hydroxides are known to decompose phosphonium salts by forming a phosphorane (**Scheme 2.13, A**). Deprotonation of the

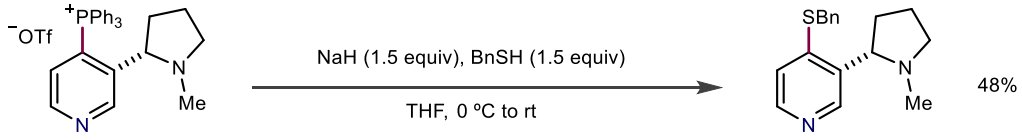
hydroxyl group forms triphenylphosphine oxide while releasing a discrete pyridyl anion. The anion, which is the most electron withdrawing ligand on the phosphorus atom, is subsequently protonated leading to the C–H product. Other potential pathways involve the formation of the alkoxyphosphorane. By either an S_N2 or E_2 mechanism triphenylphosphine oxide and the C–H product are formed (**Scheme 2.13, B and C**)



Scheme 2.13: Potential Decomposition Pathways: A) Hydroxide Attack B) E_2 C) S_N2

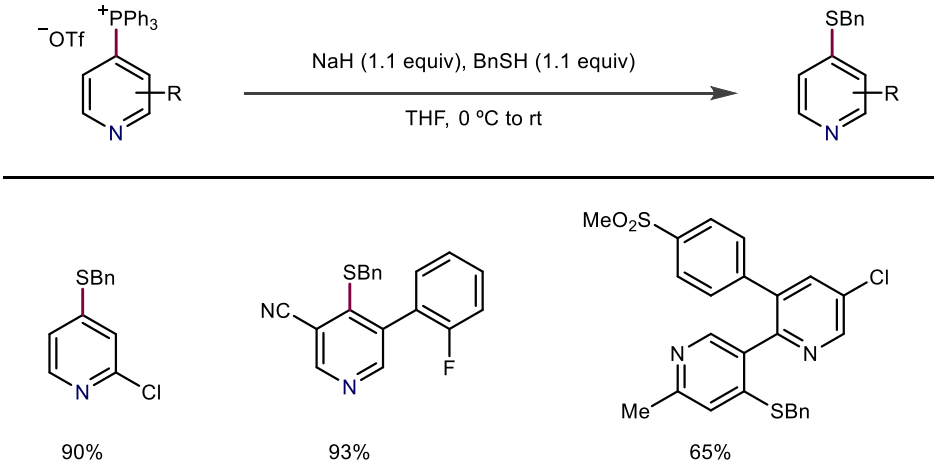
2.5 Other Nucleophiles

After successfully demonstrating heteroaryl ether formation from alkoxides, we next explored the viability of other nucleophiles in this reaction manifold. Thiolates were found to work in comparable yields using the same method. In our first publication we showed one example on nicotine (**Scheme 2.14**),[1] and Ryan Anderson, a co-worker in the McNally lab, has since expanded upon this work.



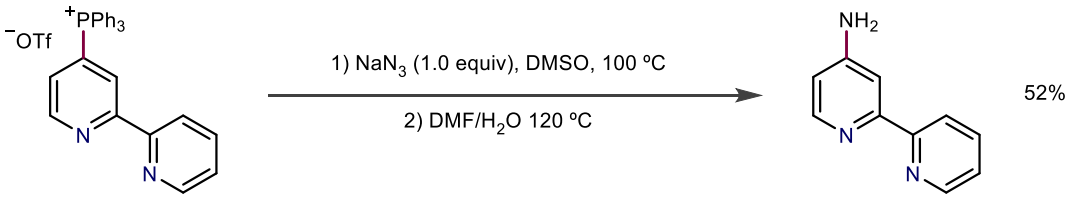
Scheme 2.14: Initial Result for Thioether Formation

Ryan optimized the reaction for thiolate nucleophiles and expanded the scope (**Scheme 2.15**).[2] Like the reaction with alkoxides, thioether formation can occur on 2-halopyridines with minimal displacement of the halide via an S_NAr process. 3,5-Disubstituted examples work with selectivity for the 4-position despite potential issues from the steric influence of the 3- and 5-position substituents. This method can be applied to pharmaceuticals as demonstrated on the example with Etoricoxib.



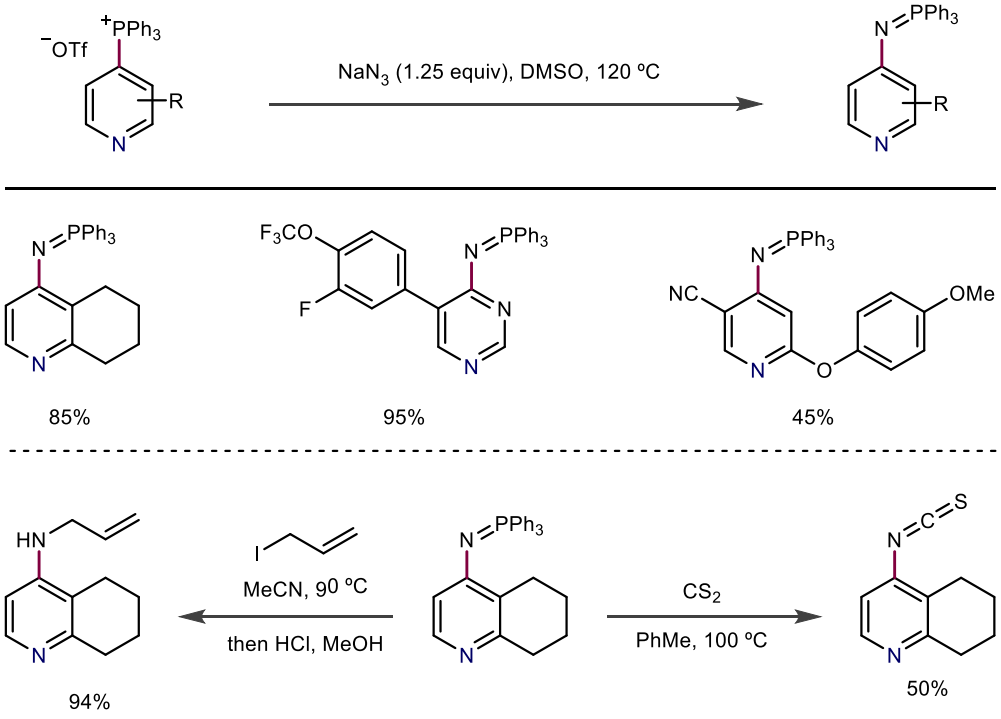
Scheme 2.15: Optimized Conditions and Scope of Thioethers

As Anders showed in his original work, azides can react with the phosphonium salts to form an iminophosphorane (**Scheme 2.4**).[19] This reaction proceeds by nucleophilic attack on the phosphonium salt either through an S_NAr reaction or by ligand-coupling to displace triphenylphosphine. The resulting heteroaryl azide then reacts with the triphenylphosphine via a Staudinger reaction. Anders' initial attempt to make an iminophosphorane from the phosphonium salts was low yielding (3%). An optimization of this reaction showed that we could achieve much higher yields. Heating the phosphonium salt of 2,2'-bipyridine in DMSO with one equivalent of sodium azide at 100 °C yields the iminophosphorane. In-situ hydrolysis of the iminophosphorane provides the amino product in reasonable yield (**Scheme 2.16**).[1]



Scheme 2.16: Iminophosphorane Formation and Hydrolysis

Chirag Patel, a co-worker in the McNally lab, optimized this reaction further, expanded the scope, and demonstrated the utility of the iminophosphorane through derivatization (**Scheme 2.17**).[3] The iminophosphorane formation is high yielding on electron-deficient substrates such as diazines and pyridines with electron-withdrawing groups. The iminophosphorane can be alkylated and then hydrolyzed to form a secondary amine. This functional group can also be reacted with carbon disulfide to install an isothiocyanate.



Scheme 2.17: Iminophosphorane Formation and Derivatization

2.6 Conclusion

The two-step approach of making a heterocyclic phosphonium salt and subsequent C–O bond formation is a useful tool in synthesizing heteroaryl ethers. This strategy is compatible with a range of pyridines and diazines. Avoiding the requirement of pre-installed halogens, this method can be applied to substrates which are difficult to halogenate and on pharmaceuticals as a way to carry out late-stage functionalization. The mechanism of heteroaryl ether formation is believed to be a stepwise ligand-coupling reaction involving the formation of a phosphorane intermediate which can be observed experimentally.

REFERENCES

(1) Hilton, M. C.; Dolewski, R. D.; McNally, A. *J. Am. Chem. Soc.* **2016**, 138, 13806

(2) Anderson, R. G.; Jett, B. M.; McNally, A. *Tetrahedron* **2018**, 74, 3129.

(3) Patel, C.; Mohnike, M.; Hilton, M. C.; McNally, A. *Org. Lett.* **2018**, 20, 2607.

(4) *WHO Model List of Essential Medicines, 19th List.*; Geneva: World Health Organization, 2015.

(5) Shah, N. D.; Fried, M. W. *Clin. Liver Dis.* **2016**, 72, 40.

(6) Lindsley, C. W. *ACS Chem. Neurosci.* **2013**, 4, 905.

(7) Mullin, J. M.; Gabello, M.; Murray, L. J.; Farrell, C. P.; Bellows, J.; Wolov, K. R.; Kearney, K. R.; Rudolph, D.; Thornton, J. J. *Drug Discovery Today* **2009**, 14, 647.

(8) Terrier, F. *Modern Nucleophilic Aromatic Substitution*, 1st ed.; Wiley.

(9) Joule, J. A.; Mills, K. *Heterocyclic Chemistry, 5th Ed*; Wiley/Blackwell Publishing Ltd, 2010.

(10) Kwan, E. E.; Zeng, Y.; Besser, H. A.; Jacobsen, E. N. *Nat. Chem* **2018**, 10, 917.

(11) Wendt, M. D.; Kunzer, A. R. *Tetrahedron* **2010**, 51, 641.

(12) Baeza, A.; Mendiola, J.; Burgos, C.; Alvarez-Builla, J.; Vaquero, J. J. *Tetrahedron Lett.* **2008**, 49, 4073.

(13) Wu, X.; Fors, B. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, 50, 9943.

(14) Enthaler, S.; Company, A. *Chem. Soc. Rev.* **2011**, 40, 4912.

(15) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, 4, 973.

(16) Harzmann, G. D.; Neuburger, M.; Mayor, M. *Eur. J. Inorg. Chem.* **2013**, 3334

(17) Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C. *Nature* **2015**, 524, 330.

(18) Lian, Y.; Coffey, S. B.; Li, Q.; Londregan, A. T. *Org. Lett.* **2016**, 18, 1362.

(19) Anders, E.; Markus, F. *Tetrahedron Lett.* **1987**, 28, 2675.

(20) Anders, E.; Markus, F. *Chem. Ber.* **1989**, 122, 119.

(21) Razuvaev, G. A.; Osanova, N. A. *J. Organomet. Chem.* **1972**, 38, 77

(22) Finet, J.-P. *Ligand Coupling Reactions with Heteroaromatic Compounds*; Pergamon, 1998; Vol. 18.

(23) Koniarczyk, J. L.; Hest, D.; Overgard, A.; Davies, I. W.; McNally, A. *J. Am. Chem. Soc.* **2018**, 140, 1990.

(24) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, 136, 10139.

(25) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. *Angew. Chem. Int. Ed.* **2014**, 53, 4802.

(26) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, 45, 546.

(27) Dukat, M.; Ramunno, A.; Banzi, R.; Damaj, M. I.; Martin, B.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2005**, 15, 4308.

(28) Xiong, H.; Hoye, A. T.; Fan, K.-H.; Li, X.; Clemens, J.; Horchler, C. L.; Lim, N. C.; Attardo, G. *Org. Lett.* **2015**, 17, 3726.

(29) A. Byrne, P.; Ortin, Y.; Gilheany, D. G. *Chem. Commun.* **2015**, 51, 1147.

CHAPTER THREE

Bis-Heterobiaryl Formation using Phosphorus Ligand-Coupling

3.1 Chapter Overview

This chapter describes the development of a new method to prepare bis-heterobiaryls through the use of phosphorus ligand-coupling. Despite the bis-heterobiaryl motif being prevalent in pharmaceuticals, their synthesis remains a challenge using conventional synthetic methods. In a three-step sequence, two heteroaromatics can be coupled together from their C–H bonds by selectively installing them on to a phosphorus reagent. By exploiting the reactivity of hypervalent phosphorus, this strategy represents one of the first synthetically useful applications of phosphorus ligand-coupling. Ben Boyle and Xuan Zhang assisted in synthesizing the bis-heterobiaryl examples to demonstrate the scope of this process. Ben Boyle performed the kinetic studies on the phosphorus ligand-coupling reaction. Professor Robert Paton and Juan Alegre-Requena carried out the computational analysis. The work presented in this chapter culminated in a publication in the journal *Science*.[1]

3.2 Background

3.2.1 Significance of Bis-Heterobiaryls

A bis-heterobiaryl is a structure possessing two heteroaromatics linked directly together through a C–C bond. This motif can be found in various pharmaceuticals and other bioactive molecules such as natural products (**Figure 3.1**). Imatinib, used in the treatment of myelogenous Leukemia, has a pyridine and pyrimidine linked directly together. Etoricoxib, used as a non-

steroidal anti-inflammatory, has a 2,3'-bipyridine within its structure.[2] MK-1064, a drug being developed for insomnia, has three pyridines linked in succession.[3] AMG-319, a potential treatment for human papillomavirus, has a quinoline and pyridine bonded together.[4] Streptonigrin[5] and Nemertelline[6] are both natural products of interest which contain this motif.

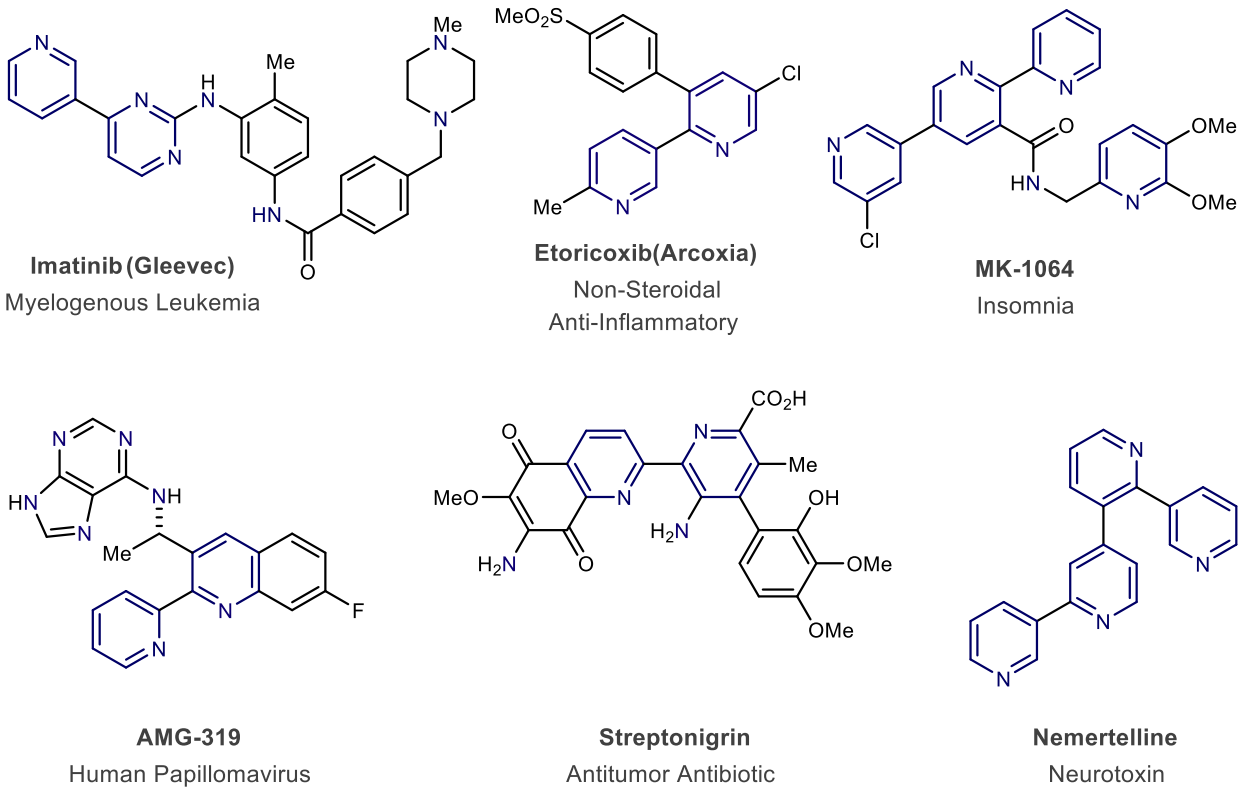


Figure 3.1: Examples of Pharmaceuticals and Bioactive Molecules Containing a Bis-Heterobiaryl

3.2.2. Synthesis of Bis-Heterobiaryls using Metal-Catalysis

An important disconnection when considering the synthesis of bis-heterobiaryls is the carbon-carbon bond connecting the two rings (**Figure 3.2**). The most common approach to construct this bond is through metal-catalysis using an electrophilic coupling partner paired up with a nucleophilic coupling partner.[7,8] The electrophilic partner is typically a (hetero)aryl halide

or triflate while the nucleophilic partner can a (hetero)aryl boronic acid, zinc, or stannane. This section will specifically cover the Suzuki-Miyaura, Negishi, and Stille cross-coupling methods.

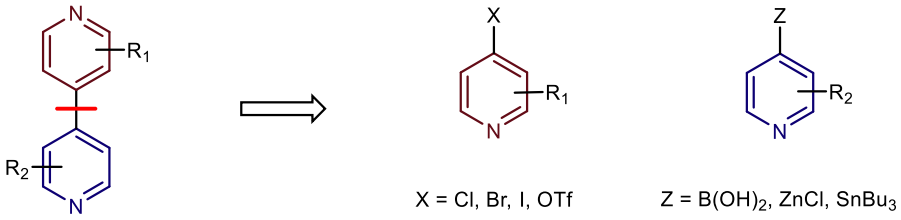
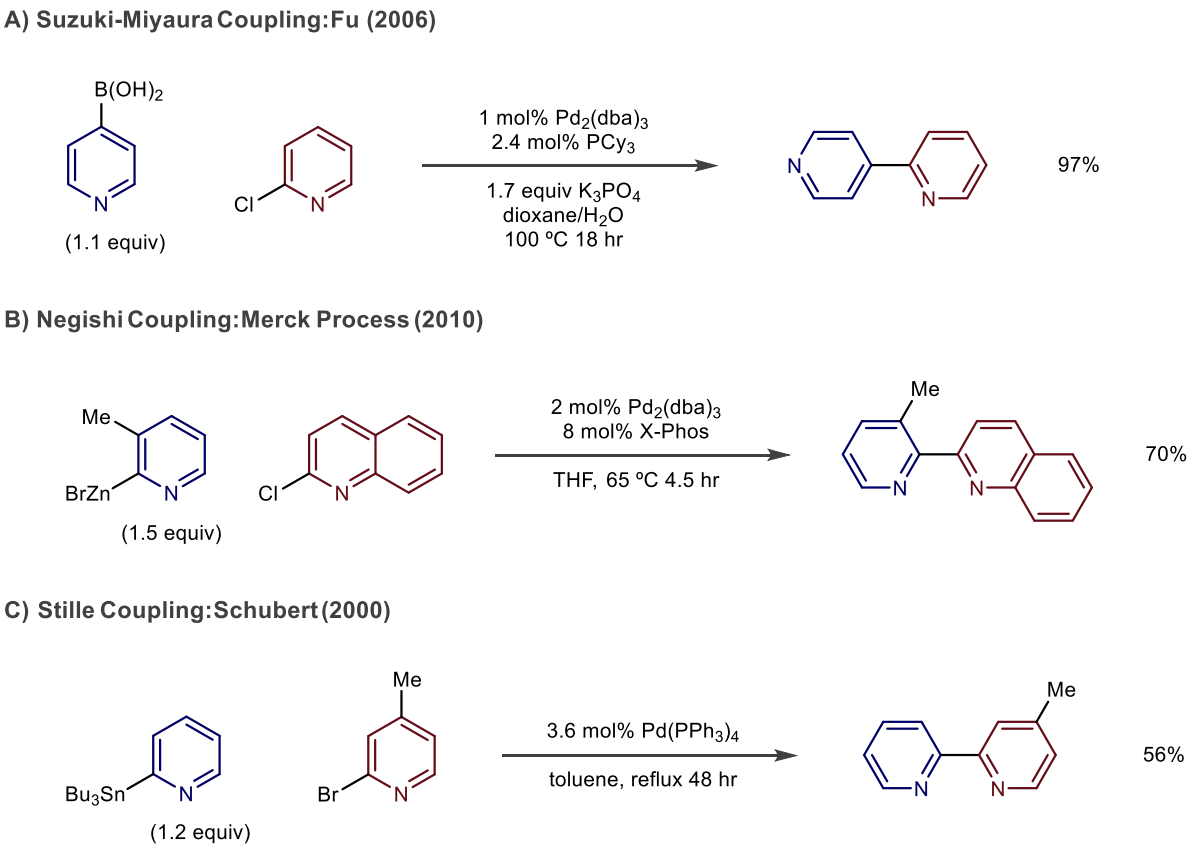


Figure 3.2: Synthesis of Bis-Heterobiaryls and Common Precursors used in Metal-Catalysis

In a Suzuki-Miyaura reaction, a (hetero)aryl halide and (hetero)aryl boronic acid are coupled using a metal catalyst.[9,10] Specific bases and ligands are generally required for the reaction to be high yielding. A representative example from the Fu group showing the synthesis of a 2,4'-bipyridine can be seen in **Scheme 3.1, A**.[10] The Suzuki-Miyaura reaction is one of the most widely used methods in the pharmaceutical industry,[11] but despite its popularity, limitations exist, especially in the synthesis of molecules containing basic functionality, such as amines. These motifs are known to interfere with catalysis by binding to the metal catalyst.[12] This issue is especially problematic when coupling two complex substrates, such as drug fragments which might have several basic nitrogen atoms. Another significant issue is the availability of the cross-coupling precursors. Building block heteroaryl halides are largely commercially available, but beyond these examples the availability is severely limited. Without required halide starting material, one is forced to carry out a halogenation reaction, which is particularly challenging on pyridines as described earlier (see **1.4.1**).[13] Heteroaryl boronic acids and similar derivatives such as boronic esters, tetrafluoroborates and MIDA boronates are significantly less available commercially when compared with the heteroaryl halide.[14] Installation of the boronic acid functionality on a heteroaromatic from the C–H bond often relies on a two-step protocol where

you must first halogenate and then convert the halogen to the desired C–B bond.[15] Lastly, boronic acids can decompose in the basic conditions typically used for a Suzuki-Miyaura coupling. This is especially true for 2-pyridyl boronic acids which are well known to be highly unstable (see **4.2.2**).[16]

Alternative metal-catalyzed cross-coupling methods include the Negishi and Stille reactions. The Negishi reaction is similar to a Suzuki-Miyaura coupling in that it utilizes heteroaryl halides and a metal catalyst but differs in the use of heteroaryl zinc reagents as an alternative to boronic acids.[17,18] The heteroaryl zinc is commonly prepared from a heteroaryl halide precursor using zinc metal or a zinc halide. While the Negishi reaction is robust, heteroaryl zincs generally suffer from a poor shelf-life and are typically prepared shortly before use.[19] A representative example from the Merck process group shows a coupling between a 2-pyridyl zinc and a chloroquinoline in **Scheme 3.1, B**.[17] The Stille reaction[20] also differs in the nucleophilic coupling partner, requiring an organostannane. Heteroaryl stannanes, which are commonly prepared from a halide precursor,[21] are more stable than their boronic acid counterparts but are toxic.[22] An example from the Schubert group shows the coupling of a 2-pyridylstannane with a 2-bromopyridine in **Scheme 3.1, C**.[23] While metal-catalyzed cross-couplings are essential reactions for the modern organic chemist, these methods are limited in their use to synthesize bis-heterobiaryls and thus there has been ongoing research to solve this problem.[7]



Scheme 3.1: Representative Examples of Metal-Catalyzed Cross-Couplings used in Bis-Heterobiaryl Synthesis

3.2.3 Synthesis of Bis-Heterobiaryls using Phosphorus Ligand-Coupling

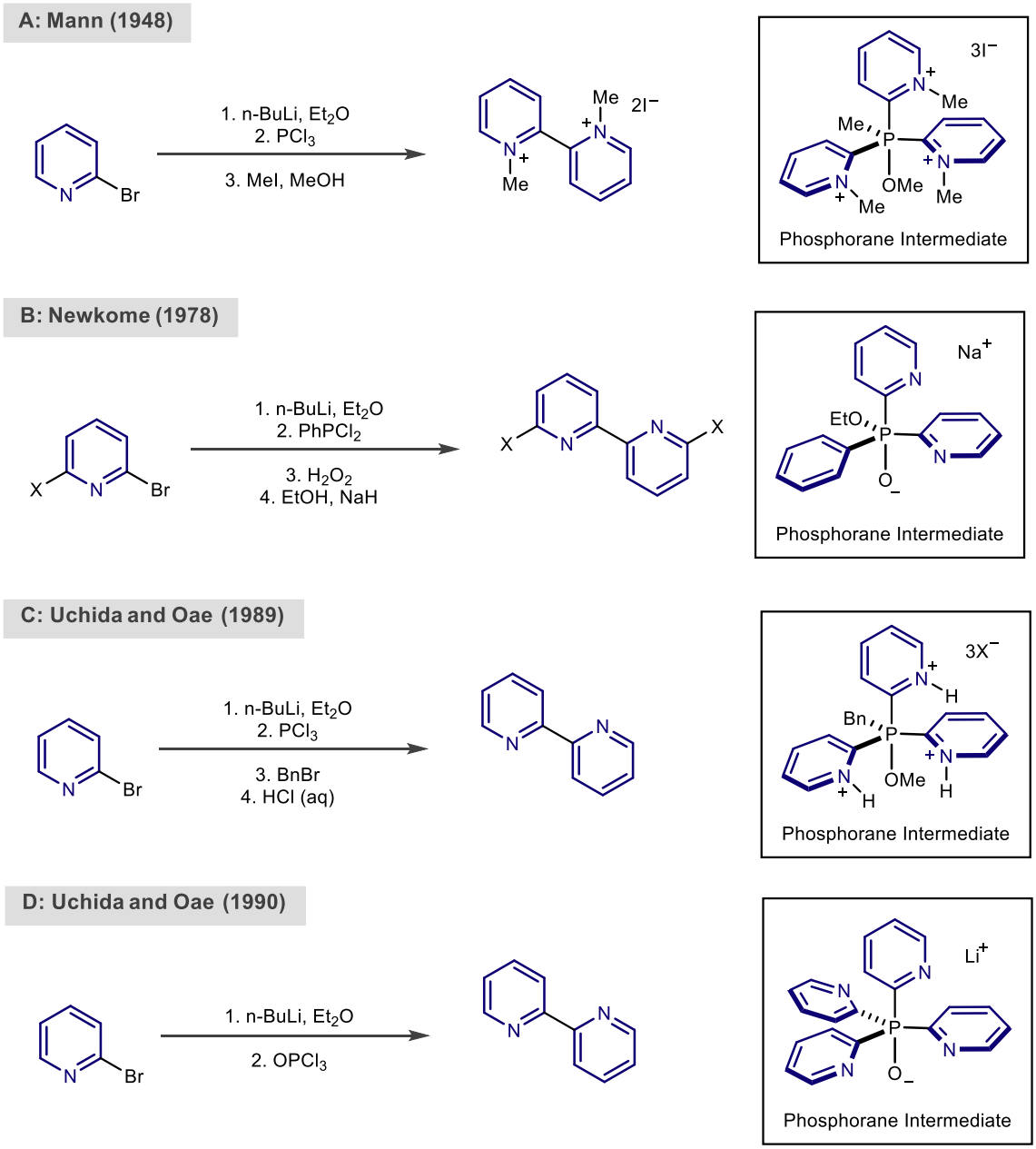
An alternative approach to metal-catalysis and significantly less explored method to synthesize bis-heterobiaryls is through phosphorus ligand-coupling. Examples from the literature typically involve the formation of 2,2'-bipyridines. Unlike metal-catalyzed reactions, phosphorus ligand-coupling requires the formation of a precursor where both the heteroaromatics are already attached to the phosphorus atom. This precursor can be a phosphonium salt or phosphine oxide with two or three pyridyl groups. The mechanism of ligand-coupling proceeds with the phosphorus atom being attacked by a nucleophile to form a P(V) phosphorane intermediate.[20] From this intermediate, two of the pyridyl groups couple while breaking their bonds to phosphorus, in a

manner akin to reductive elimination in metal-catalysis. A detailed description of this mechanism is presented later in this chapter (see section **3.4**).

The first report of bipyridine synthesis through phosphorus ligand-coupling came from Mann in 1948 (**Scheme 3.2, A**).[21] In this process, 2-bromopyridine undergoes lithium-halogen exchange and then is reacted with phosphorus trichloride to form a tripyridylphosphine. The resulting phosphine is then reacted with methyl iodide in methanol to yield a bis-methylated bipyridinium. This transformation likely occurs by methyl iodide alkylating both of the nitrogen atoms of the pyridines and the phosphorus atom to form a phosphonium salt. Methanol attacks the phosphonium salt to form a phosphorane intermediate, which then undergoes ligand-coupling to give the bipyridinium product. Thirty years later, Newkome would report a different approach for phosphorus ligand-coupling (**Scheme 3.2, B**).[22] In this example, a dipyridylphosphine is formed from dichlorophenylphosphine reacting with a lithiated pyridine. The resulting phosphine is then oxidized with hydrogen peroxide to form a phosphine oxide. An alkoxide attacks the phosphine oxide to form an alkoxy-phosphorane intermediate which then undergoes ligand-coupling.

In 1989, Uchida and Oae demonstrated an approach involving the formation of a tripyridylphosphine, which was then alkylated with benzyl bromide to yield a phosphonium salt (**Scheme 3.2, C**).[23] Addition of acidic water forms a phosphorane intermediate after the attack of water on the phosphorus atom. The phosphorane then selectively couples the pyridyl groups. A year later, Uchida and Oae developed another route to the bipyridine by reacting lithiated pyridine with phosphoryl chloride. A tripyridylphosphine oxide forms and undergoes attack by another lithiated pyridine to form a phosphorane before yielding the bipyridine via ligand-coupling (**Scheme 3.2, D**). While these seminal reports showed potential use in organic synthesis, little was done in this area. These methods are limited with the use of highly reactive butyl lithium and have

only been demonstrated to work to form dimer products. Our group believed that phosphorus ligand-coupling could be developed beyond these initial reports into a viable alternative to metal-catalyzed cross-couplings in the synthesis of bis-heterobiaryls.

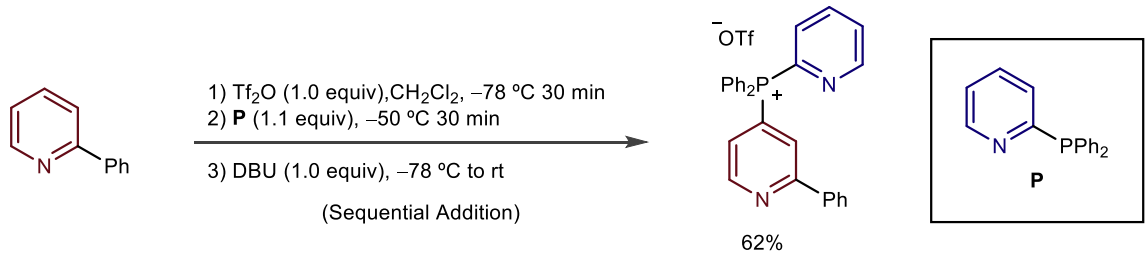


Scheme 3.2: Seminal Reports of Phosphorus Ligand-Coupling

3.3 Results and Discussion

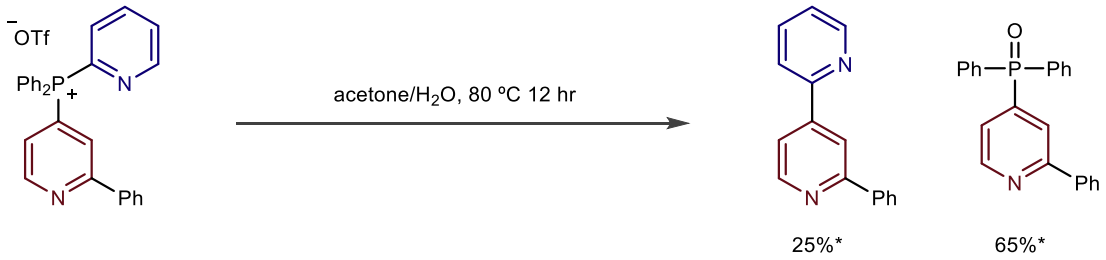
3.3.1 Initial Ligand-Coupling Results

In our initial report on heterocyclic phosphonium salts, we were able to selectively make C–P bonds on various pyridines and diazines (see **2.3.1**).[24] With the knowledge of the previously reported phosphorus ligand-coupling reactions in mind, we next looked at installing a second heteroaryl group onto the phosphorus atom. We envisioned this was achievable replacing triphenylphosphine, used in stage 2, with a heteroaryl phosphine (**P**). By sequential addition of triflic anhydride (Tf_2O), 2-pyridyl phosphine, and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) to 2-phenylpyridine, a bis-heterobiaryl phosphonium salt was formed in 62% yield (**Scheme 3.3**). The heteroaryl phosphines were found to work in comparable yields to the reactions using triphenylphosphine.



Scheme 3.3: Initial Bis-Heterobiaryl Phosphonium Synthesis

Following the synthesis of the bis-heterobiaryl phosphonium salt, we next looked towards developing the ligand-coupling reaction. Initially, the bis-heterobiaryl phosphonium salt was reacted in 1:1 acetone/water mixture[25] at 80 °C (**Scheme 3.4**). This resulted in the formation of 2'-phenyl-2,4'-bipyridine in 25% yield and a pyridyl phosphine oxide in 65% yield through an undesired pathway similar to the decomposition of a phosphonium salt shown in **Scheme 2.13, A**.[26]



*Yields were determimed using ^{1}H NMR and 1,3,5-trimethoxybenzene as an internal standard

Scheme 3.4: Initial Ligand-Coupling Result

3.3.2 Development of the Ligand-Coupling Conditions

Our initial result for phosphorus ligand-coupling had provided the desired bipyridine product and showed that ligand-coupling could be developed further. We next reacted the bis-heterobiaryl phosphonium salts with methanol, but this gave no product formation and little to no conversion of the phosphonium salt starting material. When two equivalents of anhydrous HCl was used in combination with methanol the product yield increased to 76%. To optimize the reaction, we first tested a variety of alcohols (**Table 3.1**). Isopropyl alcohol, tertbutyl alcohol, trifluoroethanol, and hexafluoroisopropanol were all found to be effective, albeit in lower yields ranging from 51% to 68%. Lowering the amount of acid to 1.0 and 0.5 equivalents gave lower yields of 62% and 48%, respectively. Lowering the temperature to 60 °C gave a yield of 44%, at 40 °C gave a yield of 12% and at room temperature there was no reactivity. Ethanol was found to give a comparable yield of 70% and was preferable to methanol due to the higher boiling point. A further improvement in yield to 80% was achieved by increasing the concentration from 0.2 M to 0.4 M. Increasing the concentration further was not found to improve the reaction. Triflic acid (TfOH) was found to work in a comparable yield to HCl while weaker acids such as trifluoroacetic acid performed poorly. The optimized conditions for ligand-coupling were found to be 80 °C in ethanol (0.4 M) with two equivalents of acid (HCl or TfOH).

Table 3.1: Optimization of the Ligand-Coupling Reaction

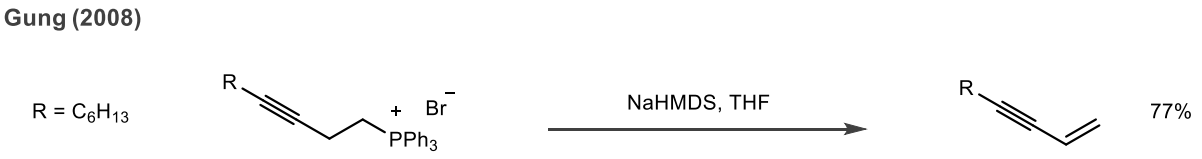
Entry	Solvent	HCl (equiv)	Temperature (°C)	Concentration (M)	% Product
1	MeOH	-	80	0.2	0
2	MeOH	2.0	80	0.2	76
3	IPA	2.0	80	0.2	57
4	TBA	2.0	80	0.2	51
5	TFE	2.0	80	0.2	59
6	HFIPA	2.0	80	0.2	68
7	MeOH	1.0	80	0.2	62
8	MeOH	0.5	80	0.2	48
9	MeOH	2.0	60	0.2	44
10	MeOH	2.0	40	0.2	12
11	EtOH	2.0	80	0.2	70
12	**EtOH**	**2.0**	**80**	**0.4**	**80**
13	EtOH	2.0	80	1.0	80

Yields based on ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

3.3.3 Development of the Fragmentable Phosphine

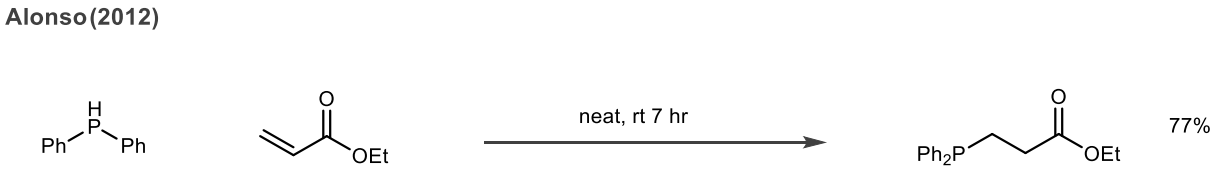
After our initial result using 2-pyridylphosphine, we sought to make different heteroaryl phosphines which were not commercially available. Pyridyl phosphines can be prepared by reacting a pyridyl lithium with chlorodiphenylphosphine[27] or through metal-catalysis using a pyridyl halide and diphenylphosphine as the coupling partners.[28] To avoid the requirement a pre-functionalized starting material that would limit the reaction scope, we developed a new method

where we could form the phosphine from the C–H bond of the azine. Our approach centers around the ability of certain alkyl phosphonium salts to fragment under basic conditions to form an alkene and a phosphine. An example of this fragmentation can be seen in **Scheme 3.5**.[29]



Scheme 3.5: Example of Fragmentation Under Basic Conditions

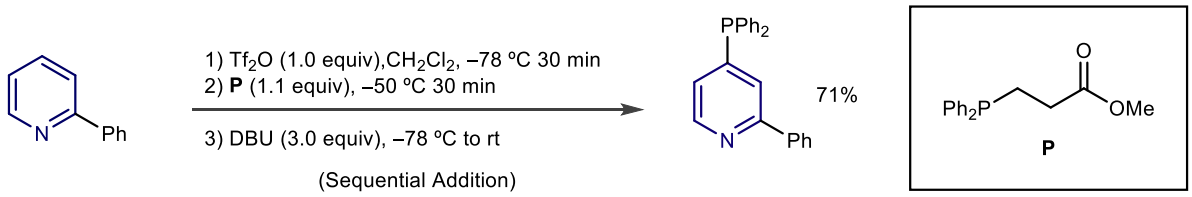
We imagined that by using a phosphine with the right alkyl linker in our salt synthesis we would form an alkyl phosphonium. This phosphonium salt could then undergo a fragmentation pathway to make a heteroaryl phosphine. A report from Alonso showed that various alkyl phosphines could be prepared from a neat reaction between diphenylphosphine and Michael acceptors (**Scheme 3.6**).[30] We believed these acrylate derived phosphines could be an effective route for heteroaryl phosphines via a modified phosphonium salt synthesis procedure.



Scheme 3.6: Synthesis of a Fragmentable Phosphine

With modifications in our standard set of conditions for the phosphonium salt synthesis,[24] we could instead form the heteroaryl phosphine. Replacing triphenylphosphine with methyl 3-(diphenylphosphaneyl)propanoate, a phosphine derived from methyl acrylate, and increasing the equivalents of DBU, we could form the heteroaryl phosphine in good yield (**Scheme 3.7**). DBU has a dual role of rearomatizing the azine (see **Int-I** in **Scheme 3.8**) after phosphine attack to form

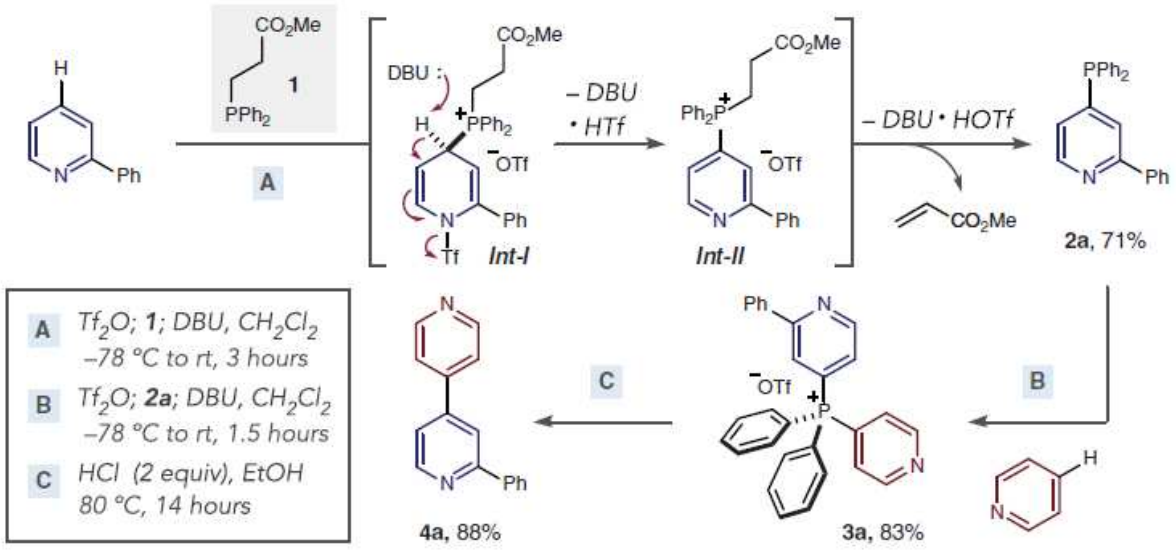
an alkyl phosphonium salt (see **Int-II** in **Scheme 3.8**) and then initiating an elimination reaction likely via an E_{1CB} mechanism to form the desired heteroaryl phosphine. Methyl acrylate is released as a byproduct from this reaction. Development of these conditions allowed us to leverage our previous scope of heteroaryl phosphonium salts as heteroaryl phosphines.



Scheme 3.7: Heteroaryl Phosphine Synthesis using the Fragmentable Phosphine

3.3.4 Scope of Bis-Heterobiaryl Synthesis

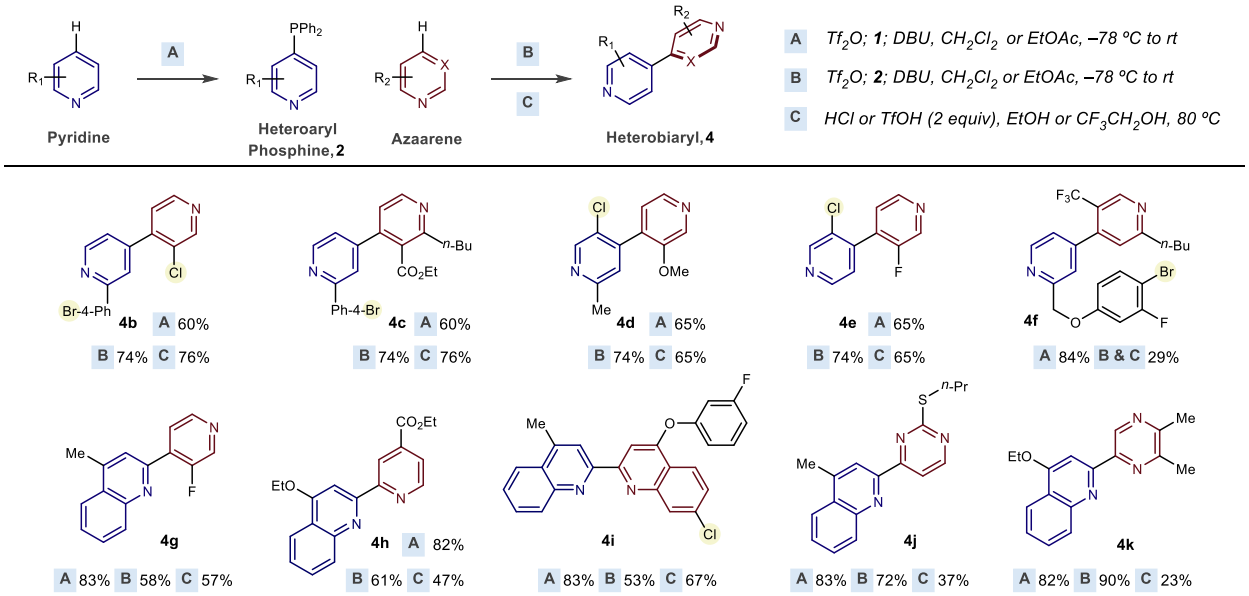
From the C–H bonds of two different pyridines or diazines we could make a bis-heterobiaryl in a 3-step process (**Scheme 3.8**). In step **A**, a heteroaryl phosphine is formed from the sequential addition Tf_2O, fragmentable phosphine (**1**), and DBU to a pyridine. In step **B**, a different pyridine can be used. Sequential addition of Tf_2O, the heteroaryl phosphine (**2a**) and DBU forms the bis-heterobiaryl phosphonium salt. In step **C**, the salt is subjected to 2 equivalents of anhydrous HCl in ethanol then heated to 80 °C to form the bis-heterobiaryl.



From S*cience*, **2018**, *362*, 799. Reprinted with permission from AAAS

Scheme 3.8: Optimized Conditions to Make Bis-heterobiaryls

Using an optimized set of conditions, we then examined the scope of bis-heterobiaryls (**Scheme 3.9**). From our initial result, we demonstrated that we could make 2,4'-bipyridines. We next showed that this strategy could be applied to make 4,4' and 2,2' systems with pyridines or quinolines. Given the highly selective nature of the phosphonium salt reaction, the 4-position of the pyridine or quinoline must be blocked to gain access to the 2-position. Pyrimidines and pyrazines worked as well, but in a lower yield for the coupling step. The reaction allows for electron-donating groups (**4d**) as well as electron-withdrawing groups (**4c**) on the azine ring. Importantly, we can have halogens such as bromines (**4b**) and chlorines (**4i**) which is significant because they can be competing sites of reactivity in metal-catalyzed cross-couplings. Medicinally relevant fluoro (**4g**) and trifluoromethyl groups (**4f**) can be present on the pyridine ring.

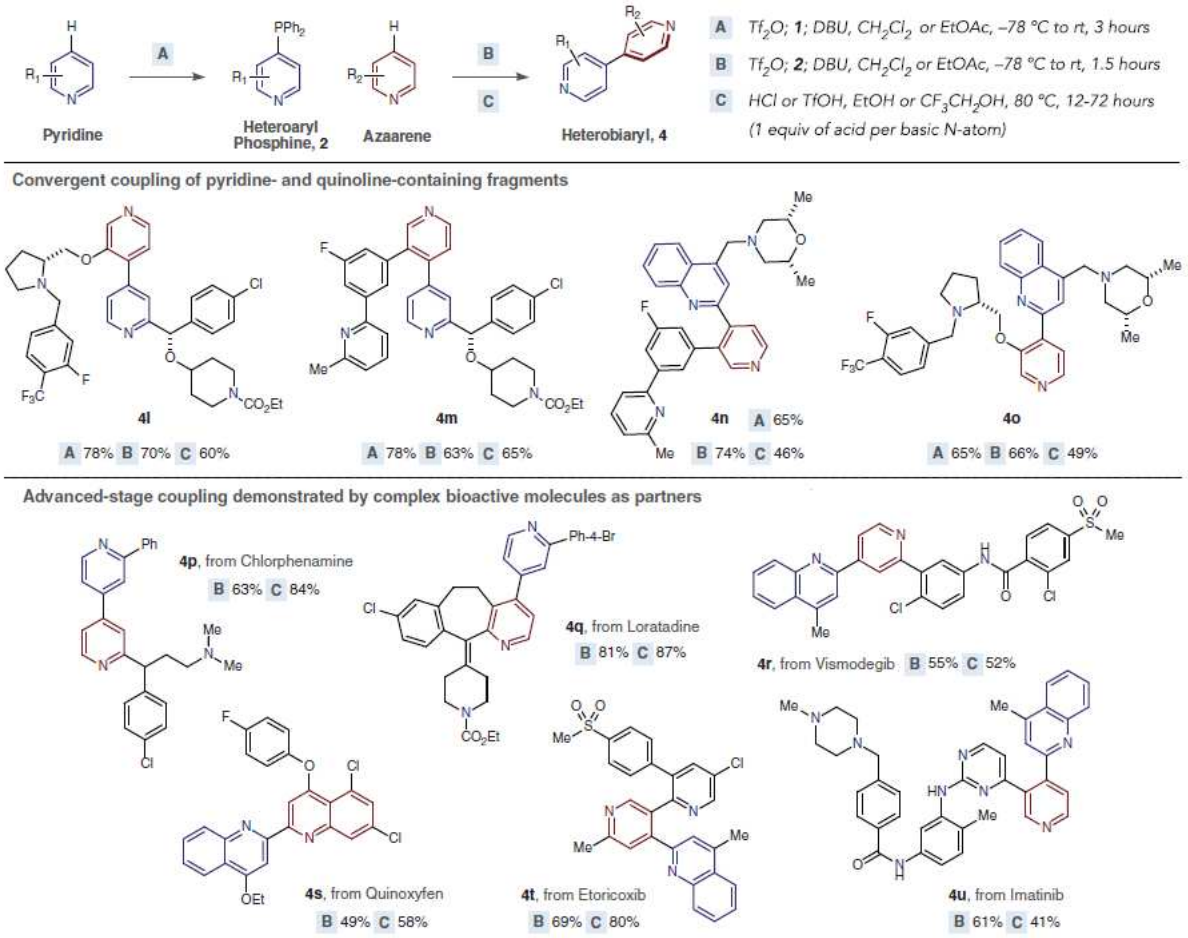


From S*cience*, **2018**, *362*, 799. Reprinted with permission from AAAS

Scheme 3.9: Bis-heterobiaryls from Building Block Substrates

After applying this process on various building block substrates, we sought to demonstrate the method on substrates where metal-catalysis would be challenging, or the coupling partners would be difficult to synthesize. We prepared four azines which are similar to drug fragments that a medicinal chemist might encounter (**4l-4o**). These azines have a high number of basic functionality and would pose a problem for metal-catalysis via poisoning of the catalyst. In addition, halogenating or borylating these structures to make the required coupling precursors would be extremely challenging. An additional complication is the multiple reactive sites, which would make it difficult to control selectivity. Using our method, we can selectively make C–P bonds to both the heteroaromatics to form the bis-heterobiaryl phosphonium salt, and through ligand-coupling, we can construct a bis-heterobiaryl. By utilizing this convergent coupling

strategy, one could quickly generate a library from a small number of fragments.



From S*cience*, **2018**, *362*, 799. Reprinted with permission from AAAS

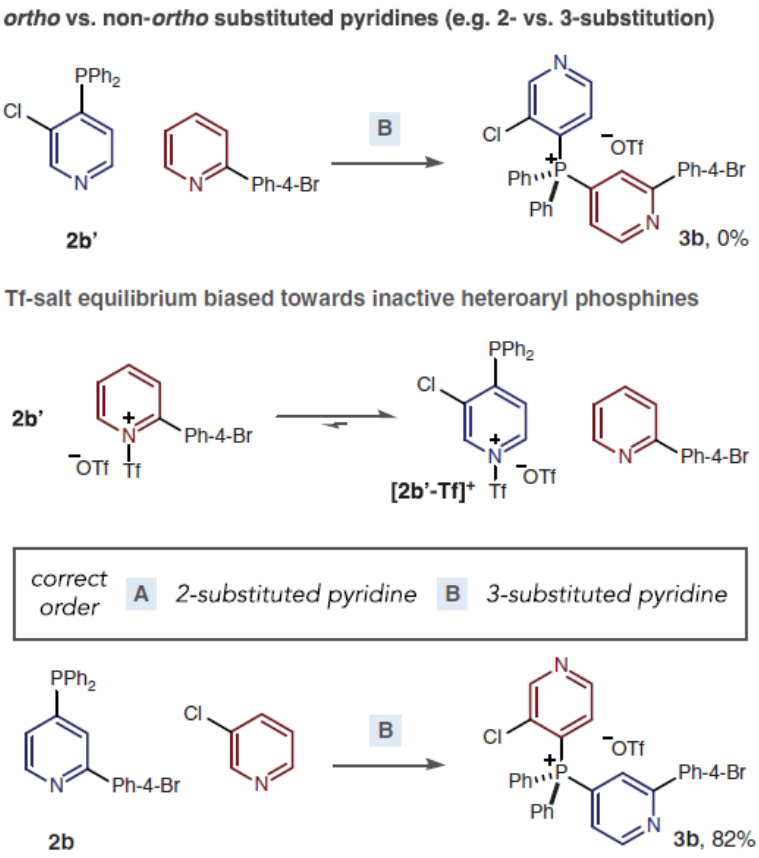
Scheme 3.10: Coupling of Complex Fragments and Bioactive Molecules

The three-step process to make bis-heterobiaryls is also applicable on pharmaceuticals and drug candidates themselves (**Scheme 3.10**). While installing a heteroaryl group on a preexisting pharmaceutical would likely not be useful in a late-stage functionalization strategy, this process could see use later in a drug's synthesis. Late-stage functionalizations are most useful when small incremental changes can be made to the bioactive compound. Addition of a pyridine, for example, would represent a relatively large change to the molecule. Using ligand-coupling in a drug's

synthesis is advantageous in that it circumvents issues of metal contamination which is relevant in many cross-coupling methods. Use of metals is generally not detrimental in the early steps of a route as there could be multiple subsequent purifications. Later in the synthesis, this is problematic as the metal could be difficult to remove completely.

3.3.5 Important Considerations in Reaction Planning

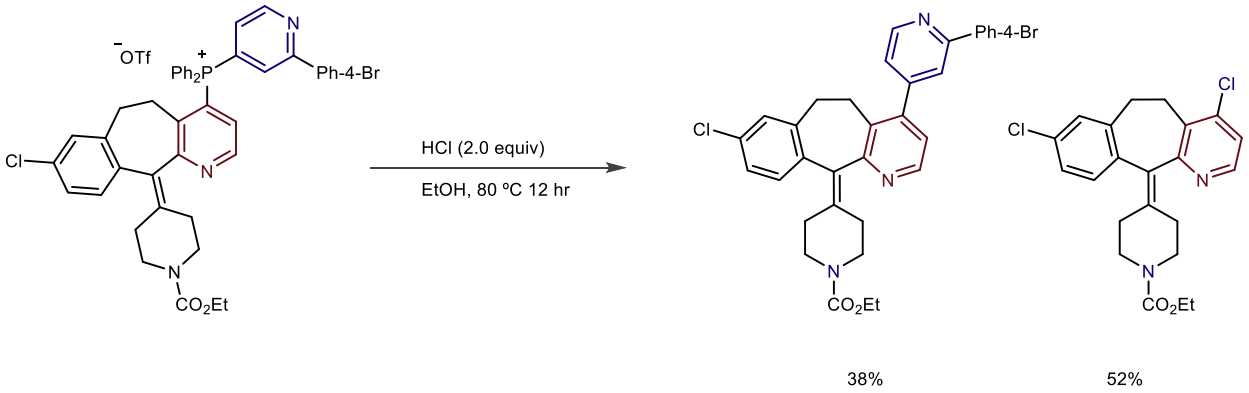
The order of addition onto the phosphorus atom can be vital when making the bis-heterobiaryl phosphonium salt. This is relevant when there is a large steric difference at the 2-position of two different pyridines. In example **4b,** the 2-arylpyridine was made into a pyridyl phosphine which was then reacted with 3-chloropyridine to make the bis-heterobiaryl phosphonium salt in 82% yield. When the order is switched and the 3-chloropyridine is made into the pyridyl phosphine first, the following reaction fails to yield the phosphonium salt (**Scheme 3.11**). The explanation for this result is that the triflyl group can exchange between the pyridines. The steric influence at the 2-position causes there to be an unfavorable equilibrium where the triflyl group is activating the wrong pyridine, and thus the reaction cannot proceed. In example **4b** it is necessary to make the 2-substituted pyridine the phosphine first for there to be a favorable equilibrium in the formation of the triflyl pyridinium in step **B**.



From S*cience*, **2018**, *362*, 799. Reprinted with permission from AAAS

Scheme 3.11: Importance of the Order of Addition onto the Phosphorus Atom

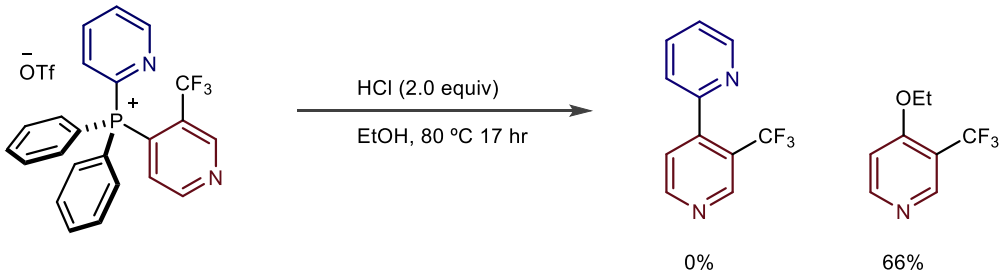
Another important consideration when carrying out ligand-coupling is the choice of acid and the number of equivalents used. In many examples, HCl and TfOH worked to give comparable yields, but in some cases, there was a large difference. When a pyridine has a bulky substituent at the 3- or 5-position or electron withdrawing groups an undesired chlorination reaction could occur during step **C** when HCl was used. In an example featuring Loratadine, chlorination was a competing reaction with the desired ligand-coupling reaction (**Scheme 3.12**).



Yields based on ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

Scheme 3.12: Unexpected Chlorination in the Ligand-Coupling Step from HCl

In some cases, the chlorination product was not observed, but instead, a heteroaryl ether formed from a sequential S_NAr reaction with ethanol and the chloropyridine (**Scheme 3.13**). To prevent these undesired pathways, TfOH can be used instead of HCl, as triflate is a non-nucleophilic counter anion. Lastly, the equivalents of acid used should equal the number of basic nitrogen atoms. For example, in **4l** we used three equivalents of triflic acid. A lower number will result in a slower rate for the reaction.



Yields based on ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

Scheme 3.13: Unexpected Ethanolysis in Ligand-Coupling Step from HCl

3.3.6 Limitations of the Bis-Heterobiaryl Synthesis

While the method to synthesize bis-heterobiaryls was found to be relatively robust, we did encounter some examples which were low yielding or failed outright (**Figure 3.3**). Steps **A** and **B** have the same limitations as they go through a similar mechanism. 2,6-Disubstituted pyridines are low yielding (<5%) for phosphonium salt formation, which is thought to be due to the influence of the ortho groups on the formation of the trifyl pyridinium. 2-Trifluoromethylpyridines also do not work well for similar reasons. Alkyl amides are not suitable for these reactions as they can react with the Tf_2O. 4-Alkyl and 4-arylpyridines generally work poorly (<25%) but the reason for this is not fully understood.

In step **C**, 2-halopyridines did not work well as there was competing an S_NAr reaction with the alcohol. 2-Methoxypyridine suffered from dealkylation when HCl and ethanol were used. When TfOH and TFE were used instead, the reaction rates were found to be slow and full conversion of the starting material was not achieved after several days. Cyano groups were also found to react in HCl and ethanol and coupling was slow in TfOH and TFE. Esters could be tolerated but would undergo transesterification. 3-Bromo and 3-iodopyridines would dehalogenate while chloro and fluoro variants worked well.

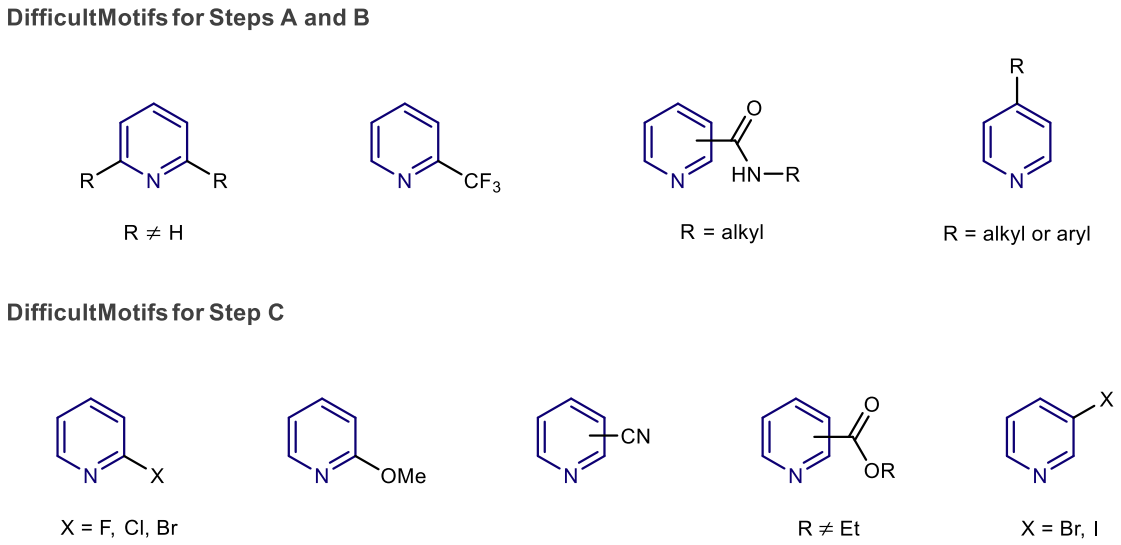
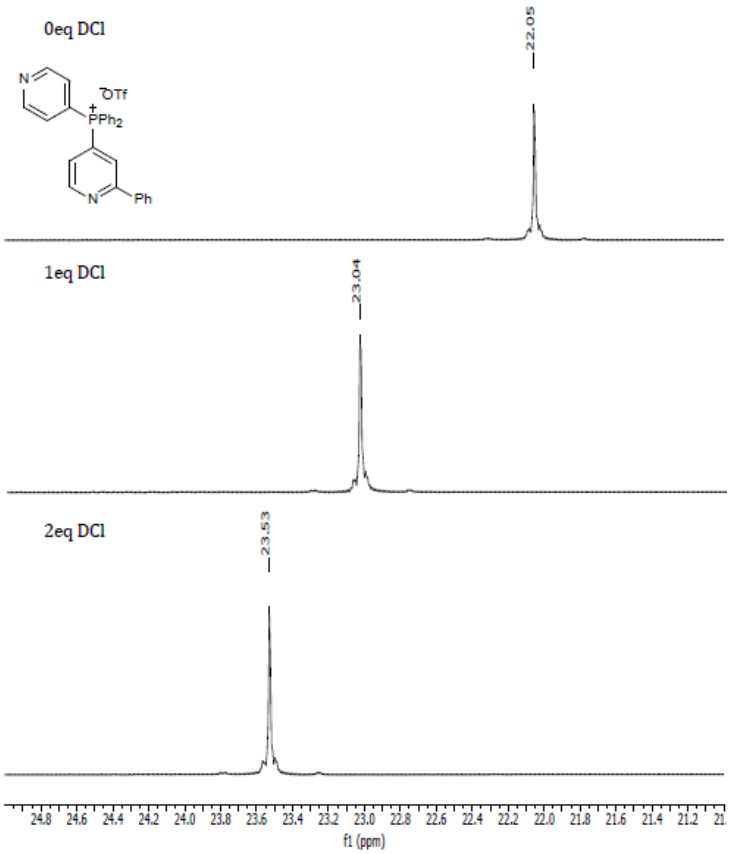


Figure 3.3: Difficult Substrates for Bis-Heterobiaryl Synthesis

3.4 Mechanism

3.4.1 Experimental and Computational Probe of the Mechanism

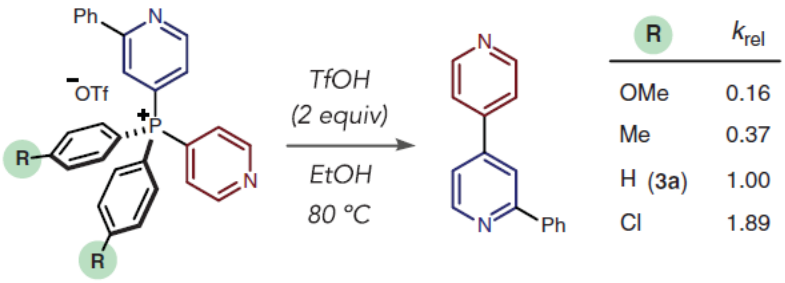
The mechanism of phosphorus ligand-coupling was probed through experiment and computation. A coupling to make a 4,4'-bipyridine was used as the model system. To begin the investigation, we wished to understand the role of acid in this process. The reaction begins with the protonation of both the pyridines. This makes the phosphorus atom of the phosphonium salt more electrophilic, allowing for an alcohol to attack forming a phosphorane intermediate. The effect of the acid on the electrophilicity of the phosphorus atom can be observed by ^{31}P NMR. Each additional equivalent of acid causes the peak of the phosphonium to shift further downfield (**Scheme 3.14**).



From S*cience*, **2018**, *362*, 799. Reprinted with permission from AAAS

Scheme 3.14: Influence of Acid on the Phosphorus Chemical Shift

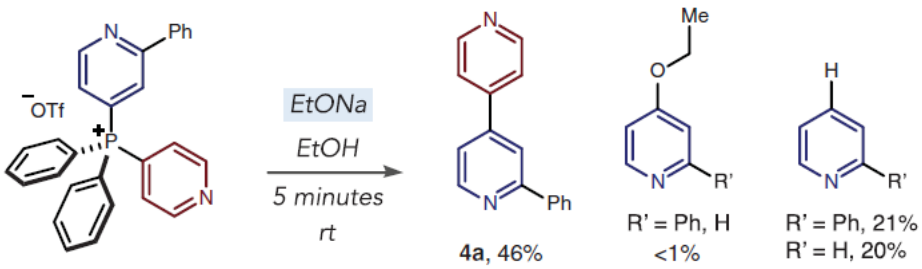
Without acid, the phosphorane does not form and ligand-coupling does not occur. This result led us to believe that the attack of the alcohol is the rate-determining step of the reaction and changing the electronics of the phosphonium salt should impact the rate of the reaction. By installing different groups at the 4-position of the aryl substituents of the phosphine we could make the phosphorus more or less electrophilic (**Scheme 3.15**). When this group is chloro the rate increases with a k_{rel} of 1.89. When this group is methoxy the rate of the reaction decreases with a k_{rel} of 0.16. This result agrees with our hypothesis that the nucleophilic attack of the alcohol is the rate-determining step in the reaction.



From S*cience*, **2018**, *362*, 799. Reprinted with permission from AAAS

Scheme 3.15: Influence of Electronics on the Rate of the Reaction

Additional evidence that the attack of the alcohol is the rate-determining step comes from reacting the phosphonium salt with an alkoxide (**Scheme 3.16**). When this alternative method is used, the phosphorane forms at room temperature and the ligand-coupling reaction is complete within 5 minutes. When the acidic conditions are used ligand-coupling does not occur until 40 °C and the rate is relatively slow even at 80 °C requiring several hours to go to completion.

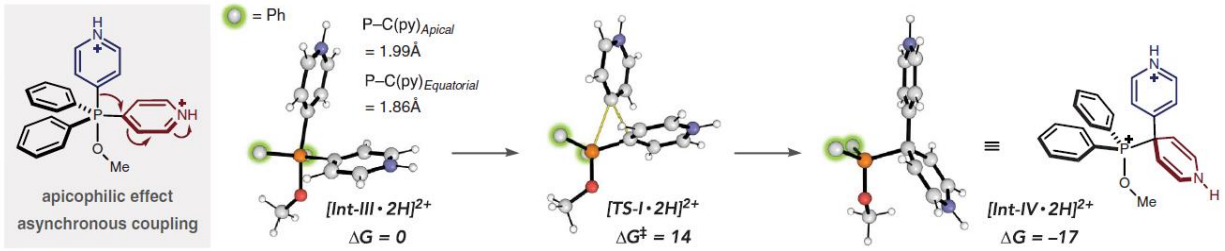


From S*cience*, **2018**, *362*, 799. Reprinted with permission from AAAS

Scheme 3.16: Ligand-Coupling via an Alkoxide Nucleophile

To gain further insight, we collaborated with the Paton lab to probe the mechanism using computation. Their study indicates that once the phosphorane (**Int-III**) forms, there is a trans-effect that weakens the C–P bond of the apical pyridine and there is a buildup of electron density on this ring. This weakening is reflected in the computed bond lengths with the apical pyridine

C–P bond being 1.99 Å vs the equatorial pyridine C–P bond being 1.86 Å (**Scheme 3.17**). The apical pyridine can migrate on to the protonated equatorial pyridine as electron density from the C–P σ bond is donated in the π* of the aromatic ring. The protonated equatorial pyridine serves as a good acceptor for this buildup of negative charge. This migration goes through a transition state (**TS-1**) with three-center, four-electron bonding between the pyridyl groups and the phosphorus atom. The energy barrier of this process is 14 kcal/mol and after the migration, a dearomatized intermediate (**Int-IV**) forms and elimination of methyl diphenylphosphinite regains aromaticity by forming the bis-heterobiaryl.



From S*cience*, **2018**, *362*, 799. Reprinted with permission from AAAS

Scheme 3.17: DFT Calculated Transition State for Ligand-Coupling Reaction

3.4.2 Rationalization of Selectivity During Phosphorus Ligand-Coupling

The computational study also provided insight into the selectivity of the reaction. From the phosphorane intermediate (**Int-III**) it is possible for a phenyl or the alkoxy group to migrate but experimentally only the heteroaryl groups were observed to couple. The phosphorane can have different conformations which can interchange through a Berry pseudorotation.[31,32] The most stable phosphorane has the most electron-withdrawing groups in the apical positions.[33] The lowest energy conformation places a protonated pyridine and alkoxy group in these apical positions and the two phenyls and the other protonated pyridine occupy the equatorial positions. A trans-effect

weakens the C–P of the aromatic opposite the alkoxy group, resulting in a buildup of negative charge on the ring. The protonated pyridine is more effective at stabilizing the electron density as opposed to a phenyl group. The apical pyridine can be viewed as the donor group which will then migrate on to the acceptor group in the equatorial position. The acceptor can be the other protonated pyridine or one of the phenyls. For the migration to occur the electron density of the apical C–P σ bond donates into the π* of the equatorial group. The protonated pyridine can stabilize the negative charge from this donation and thus it is the acceptor group.

The selectivity was also examined through computation. The $\Delta G^{\ddagger}$ for different migrations was determined using DFT calculations (**Figure 3.4**). The energy of migration which leads to the desired bis-heterobiaryl formation was found to be 14 kcal/mol. When acid is removed from the system, $\Delta G^{\ddagger}$ increases to 30 kcal/mol. This increase in energy is rationalized by the loss of stabilization that results from protonation of the two pyridines. Phenyl migration is disfavored by 11 kcal/mol over pyridyl migration. Alkoxy migration was surprisingly close with a $\Delta G^{\ddagger}$ of 18 kcal/mol. Despite heteroaryl ether formation being known from our previous work, we did not observe this product when bis-heterobiaryl phosphonium salts were used.

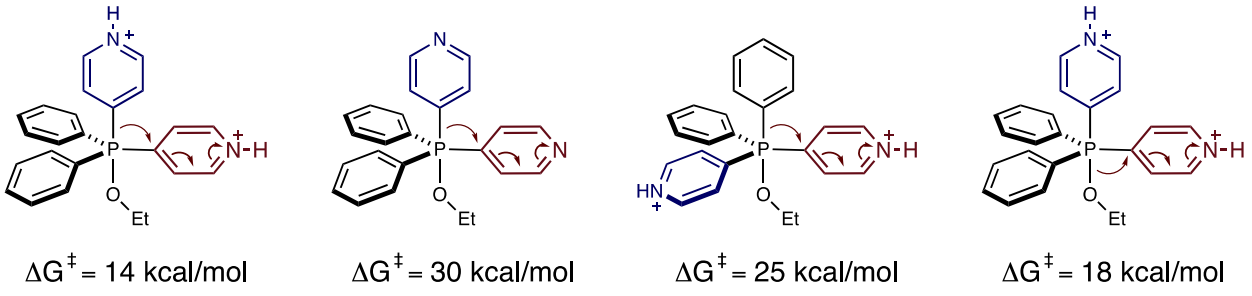


Figure 3.4: DFT Calculated $\Delta G^{\ddagger}$ for Migration of Different Groups

3.5 Conclusion

The synthesis of bis-heterobiaryls using phosphorus ligand-coupling offers an alternative to metal-catalysis. Some of the challenges associated with catalysis such as precursor synthesis, catalyst poisoning, and metal contamination can be avoided using this method. The significance of this approach was demonstrated on complex fragments and pharmaceuticals where the use of metal-catalysis would likely not be an option. The mechanism of phosphorus ligand-coupling in the synthesis of a 4,4'-bipyridines was probed through experiment and computation. Phosphorane formation by the attack of the alcohol was determined through experiments to be the rate-determining step of the reaction. Computation suggests that from the phosphorane, ligand-coupling occurs through a stepwise migration of the apical pyridine onto the equatorial pyridine followed by elimination of ethyl diphenylphosphinite to yield the bis-heterobiaryl.

REFERENCES

(1) Hilton, M. C.; Zhang, X.; Boyle, B. T.; Alegre-Requena, J. V.; Paton, R. S.; McNally, A. *Science* **2018**, 362, 799.

(2) Capdeville, R.; Buchdunger, E.; Zimmermann, J. *Nature* **2002**, 1, 493.

(3) Roecker, A. J.; Mercer, S. P.; Schreier, J. D.; Cox, C. D.; Fraley, M. E.; Steen, J. T.; Lemaire, W.; Bruno, J. G.; Harrell, M. C.; Garson, S. L.; et al. *ChemMedChem* **2014**, 9, 311.

(4) Cushing, T.; Hao, X.; Shin, Y.; Andrews, K.; Brown, M.; Cardozo, M.; Chen, Y.; Duquette, J.; Fisher, B.; Gonzalez-Lopez de Turiso, F.; et al. *J. Med. Chem.* **2015**, 58, 480.

(5) Donohoe, T. J.; Jones, C. R.; Kornahrens, A. F.; Barbosa, L. C. A.; Walport, L. J.; Tatton, M. R.; O'Hagan, M.; Rathi, A. H.; Baker, D. B. *J. Org. Chem.* **2013**, 78, 12338.

(6) Kem, W. R.; Soti, F.; Rittschof, D. *Biomolecular Engineering* **2003**, 20, 355.

(7) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, 36, 1058.

(8) Newkome, G. R.; Patri, A. K.; Holder, E.; Schubert, U. S. *Eur. J. Org. Chem.* **2004**, 235.

(9) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, 45, 3484.

(10) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, 15, 1282.

(11) Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, 59, 4443.

(12) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. **2018**, 10, 383.

(13) Joule, J. A.; Mills, K. *Heterocyclic Chemistry, 5th Ed*; Wiley/Blackwell Publishing Ltd, 2010.

(14) Markovic, T.; Rocke, B. N.; Blakemore, D. C.; Mascitti, V.; Willis, M. C. *Chem. Sci.* **2017**, 8, 4437.

(15) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, 67, 5394.

(16) Cox, P. A.; Reid, M.; Leach, A. G.; Campbell, A. D.; King, E. J.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2017**, 139, 13156.

(17) Luzung, M. R.; Patel, J. S.; Yin, J. *J. Org. Chem.* **2010**, 75, 8330.

(18) Savage, S. A.; Smith, A. P.; Fraser, C. L. *J. Org. Chem.* 63, 10048.

(19) Colombe, J. R.; Bernhardt, S.; Stathakis, C.; Buchwald, S. L.; Knochel, P. *Org. Lett.* **2013**, 15, 5754.

(20) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, 100, 3636.

(21) Mathieu, J.; Marsura, A. *Synth Commun* **2003**, 33, 409.

(22) Chan, K.-P.; Ling, Y. H.; Chan, J. L.-T.; Loh, T.-P. *J. Org. Chem.* **2007**, 72, 2127.

(23) Schubert, U. S.; Eschbaumer, C.; Heller, M. *Org. Lett.* **2000**, 2, 3373.

(24) Hilton, M. C.; Dolewski, R. D.; McNally, A. *J. Am. Chem. Soc.* **2016**, 138, 13806.

(25) Bowen, R. J.; Fernandes, M. A.; Gitari, P. W.; Layh, M. *PHOSPHORUS-SULFUR* **2006**, 181, 1403.

(26) Koniarczyk, J. L.; Hest, D.; Overgard, A.; Davies, I. W.; McNally, A. *J. Am. Chem. Soc.* **2018**, 140, 1990.

(27) Nurttila, S. S.; Brenner, W.; Mosquera, J.; van Vliet, K. M.; Nitschke, J. R.; Reek, J. N. H. *Chem. Eur. J.* **2019**, 25, 609.

(28) Yamamoto, M.; Nakanishi, T.; Kitagawa, Y.; Fushimi, K.; Hasegawa, Y. *Materials Letters* **2016**, 167, 183.

(29) Gung, B.; Omollo, A. O. *Eur. J. Org. Chem.* **2008**, 4790.

(30) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Green Chem.* **2012**, 14, 2699.

(31) Nakazawa, H.; Kawamura, K.; Ogawa, T.; Miyoshi, K. *J Organomet Chem* **2002**, 646, 204.

(32) Wang, P.; Agrafiotis, D. K.; Streitwieser, A.; Schleyer, P. von R. *J. Chem. Soc. Chem. Commun.* **1990**, 3, 201.

(33) McDowell, R. S.; Streitwieser, A. *J. Am. Chem. Soc.* **1985**, *107*, 5849.

CHAPTER FOUR

Bis-Heterobiaryl Formation from Chloroazines

4.1 Chapter Overview

Building from our previous work on phosphorus ligand-coupling, this chapter describes an alternative approach to synthesize bis-heterobiaryls using chloroazines as coupling partners. From diphenylphosphine, two sequential S_NAr reactions on chloroazines yields a bis-heterobiaryl phosphonium salt. A new set of conditions were then employed to induce ligand-coupling to form the bis-heterobiaryl. Importantly, this approach gives access to 2,2'-bipyridines which were difficult to synthesize using our previous ligand-coupling method. This work represents an advancement to the area of heterobiaryl synthesis by enabling a general and convenient coupling of abundant chloroazines without the need for specialized sets of conditions often required when using metal-catalyzed cross-couplings. Ben Boyle contributed to the discovery and optimization of this process, as well as, the preparation of a number of bis-heterobiaryl examples presented in the scope. This work has been published on the preprint server *ChemRxiv*.[1]

4.2 Background

4.2.1 Importance of 2,2'-Bipyridines

The 2,2'-bipyridine motif is a privileged motif in a variety of areas in chemistry (**Figure 4.1**). As mentioned previously, bis-heterobiaryls are found in pharmaceuticals and specifically a 2,2'-bipyridine can be found in the structure of the drug candidate MK-1064 (**Figure 3.1**).[2] Caerulomycin C, an antibiotic natural product produced by *Streptomyces caeruleus*, features this

motif.[3] Bipyridines can also be found in a variety of different material applications such as OLEDs,[4] metallosupramolecular assemblies,[5] and nanomaterials.[6] Importantly, 2,2'-bipyridines are ligands in metal complexes commonly used in organic synthesis.[7]

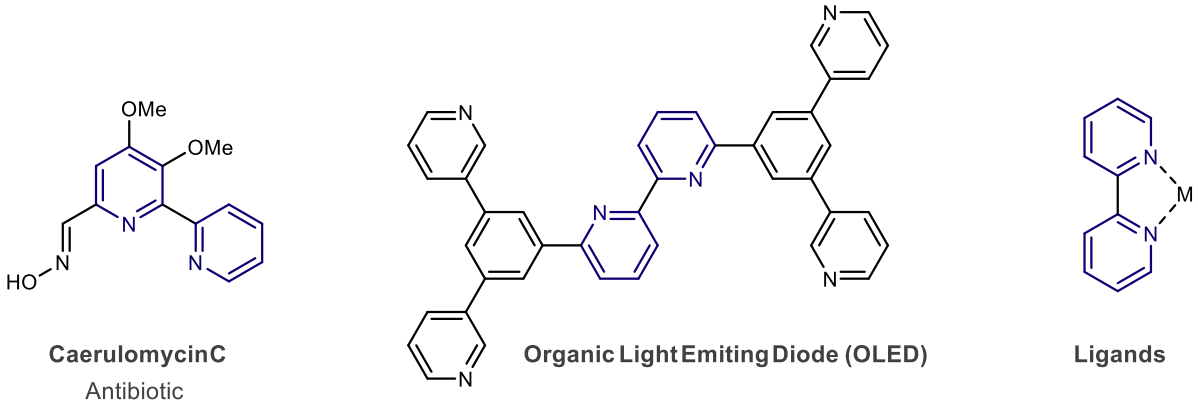
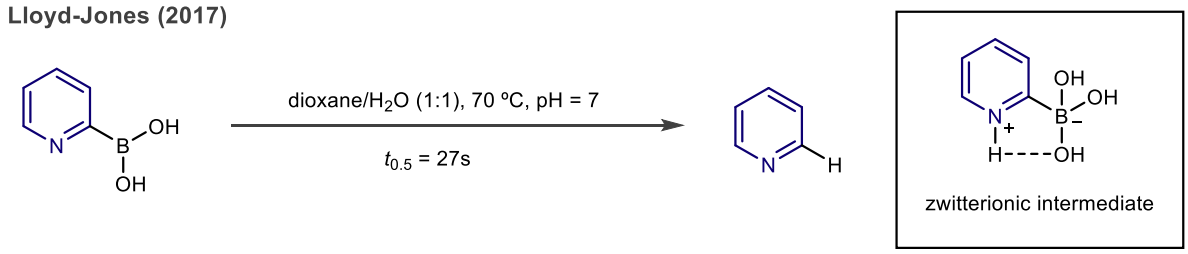


Figure 4.1: 2,2'-Bipyridines Found in Different Areas of Chemistry

4.2.2 New Approaches to 2,2'-Bipyridine Synthesis

The most common approach to synthesize unsymmetrical 2,2'-bipyridines is through metal-catalyzed cross-couplings.[6] While the Suzuki–Miyaura, Negishi and Stille couplings are some of the most widely used reactions for biaryl synthesis, their application in the synthesis of 2,2'-bipyridine has not been as extensively studied. The Suzuki-Miyaura coupling has the most difficulties in this aspect as the required 2-pyridyl boronic acid is often unstable in the typical reaction conditions. This creates a significant challenge in applying this reaction for 2,2'-bipyridine synthesis. The mechanism for this decomposition has been extensively studied by the Lloyd-Jones group. They found that in neutral conditions at 70 °C the half-life of the 2-pyridyl boronic acid is just 27 seconds (**Scheme 4.1**).[8] The decomposition occurs via protodeboronation where the carbon-boron bond is cleaved and subsequently protonated via a zwitterionic

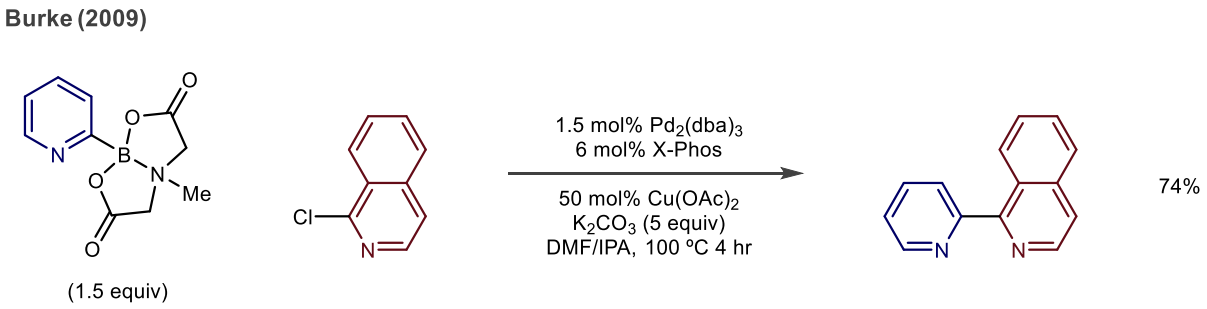
intermediate.[9] The N-H bond of the pyridine interacts with the borate to stabilize the zwitterionic intermediate, promoting this decomposition pathway.



Scheme 4.1: Protodeboronation of 2-Pyridyl Boronic Acids via Zwitterionic Intermediate

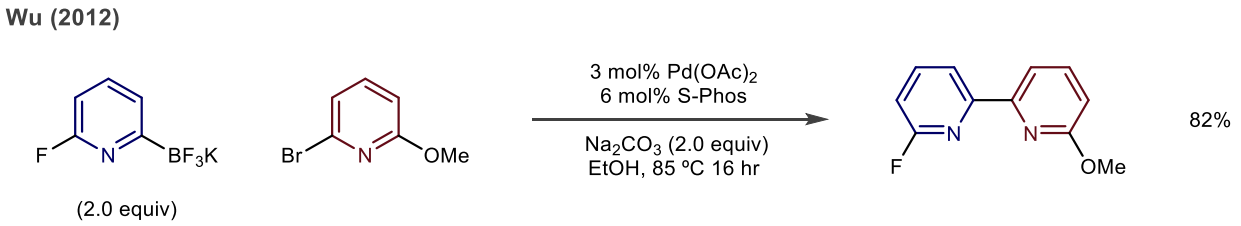
The unreliability of 2-pyridyl boronic acids has been an issue in the pharmaceutical industry where the Suzuki-Miyaura coupling is commonly used. In a survey of electronic notebooks from Pfizer, couplings using these reagents showed a very poor success rate with only 28 out of 358 reactions giving a yield higher than 20%.[10]

To address this deficiency in the Suzuki-Miyaura coupling, many groups have worked towards creating boronic acid equivalents. One example is the MIDA boronate developed by the Burke group.[11] This benchtop stable reagent slowly releases a boronic acid *in-situ*, limiting the time it can decompose in the reaction. A heteroaryl MIDA boronate can be prepared by carrying out lithium-halogen exchange on a heteroaryl halide. The resulting organolithium intermediate is then trapped with boron isopropoxide followed by *N*-methyliminodiacetic acid (MIDA). A 2,2'-coupling between 2-pyridyl MIDA boronate and 1-chloroisoquinoline is shown in **Scheme 4.2**.



Scheme 4.2: MIDA Boronate used in Bis-Heterobiaryl Synthesis

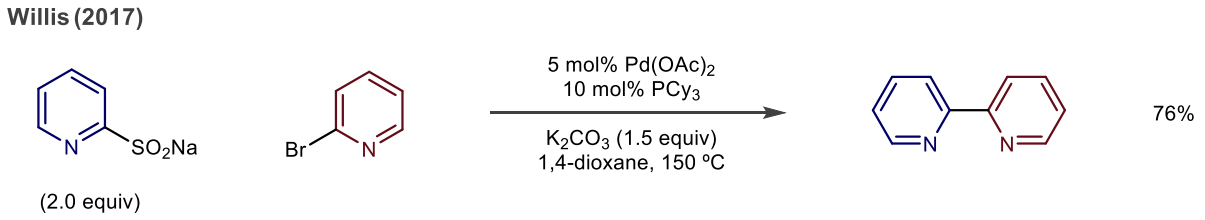
A different approach, pioneered by the Molander group, utilizes potassium trifluoroborate salts as boronic acid equivalents in metal-catalyzed cross-couplings.[12] These air-stable salts are prepared by reacting a boronic acid or ester with aqueous KHF_2. While Molander's original work indicated that the 2-pyridyl variant did not work generally, Wu later showed successful couplings involving 2-pyridyl trifluoroborates which were also 6-substituted.[13] It should be noted that 6-substituted boronic acids show much greater stability when compared with other examples (**Scheme 4.3**).[10]



Scheme 4.3: 2-Pyridyl Trifluoroborate used in Bipyridine Synthesis

Besides boronic acid derivatives, alternative partners have also been developed. An emerging method comes from the Willis group using pyridine sulfonates.[14] The sulfonates can be prepared from 2-mercapto or 2-halopyridine precursors and are benchtop stable. An example of a bipyridine synthesis using this method can be seen in **Scheme 4.4**. Despite recent advancements,

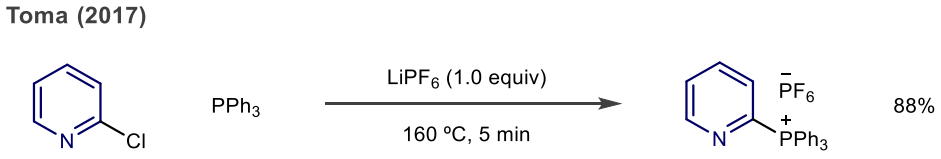
2,2'-bipyridine synthesis remains a significant challenge requiring the development of new methods.



Scheme 4.4: Pyridine Sulfonate used in Bipyridine Synthesis

4.2.3 Synthesis of Heteroaryl Phosphonium Salts via an S_NAr Mechanism

Phosphonium salts can also be prepared via a nucleophilic aromatic substitution (S_NAr) reaction between a heteroaryl halide and triphenylphosphine. In a paper from Toma, 2-halopyridines were reacted neat with triphenylphosphine at elevated temperatures (120-180 °C) to give 2-pyridyl phosphonium salts (**Scheme 4.5**).[15] While chloro, bromo, and iodopyridines worked using this method, 2-fluoropyridines failed to form the phosphonium salt. This result goes against typical S_NAr reactivity, which suggests that 2-fluoropyridines should be the most active. Inorganic salts such as LiBr and $LiPF_6$ were found to improve the yield of the reaction, although their role is not completely understood.

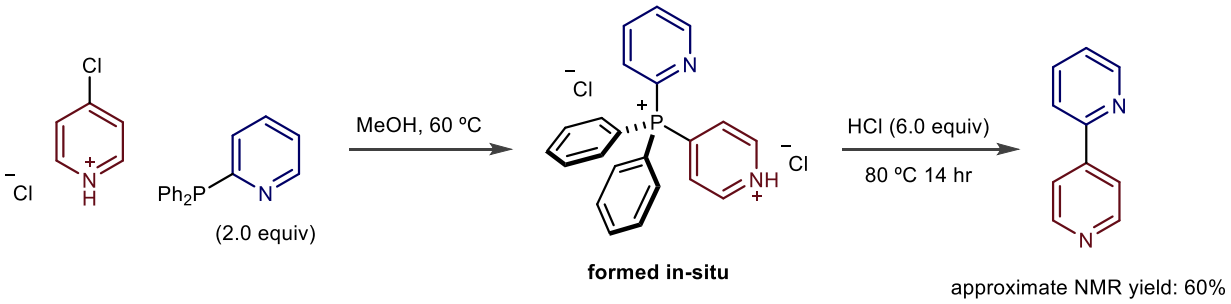


Scheme 4.5: Phosphonium Salt Synthesis via S_NAr Reaction

4.3 Results and Discussion

4.3.1 Tandem S_NAr-Ligand-Coupling Results

From our initial findings utilizing bis-heterobiaryl phosphonium salts to make bis-heterobiaryls (see chapter three), we sought to apply the ligand-coupling reaction in a new way to access compounds that we previously could not synthesize. We proposed that an S_NAr reaction would form the phosphonium salt, and then through ligand-coupling, we would make a bis-heterobiaryl. Initially, we reacted 4-chloropyridine hydrochloride with two equivalents of 2-pyridylphosphine in ethanol at 60 °C leading to the formation of a bis-heterobiaryl phosphonium salt. Protonation of the 4-chloropyrdine significantly lowers the temperature required to carry out the S_NAr reaction. After the salt formation, additional acid was then added, and the reaction was warmed to 80 °C. After 14 hours approximately 60% of the bis-heterobiaryl was formed by ^1H NMR analysis (**Scheme 4.6**).

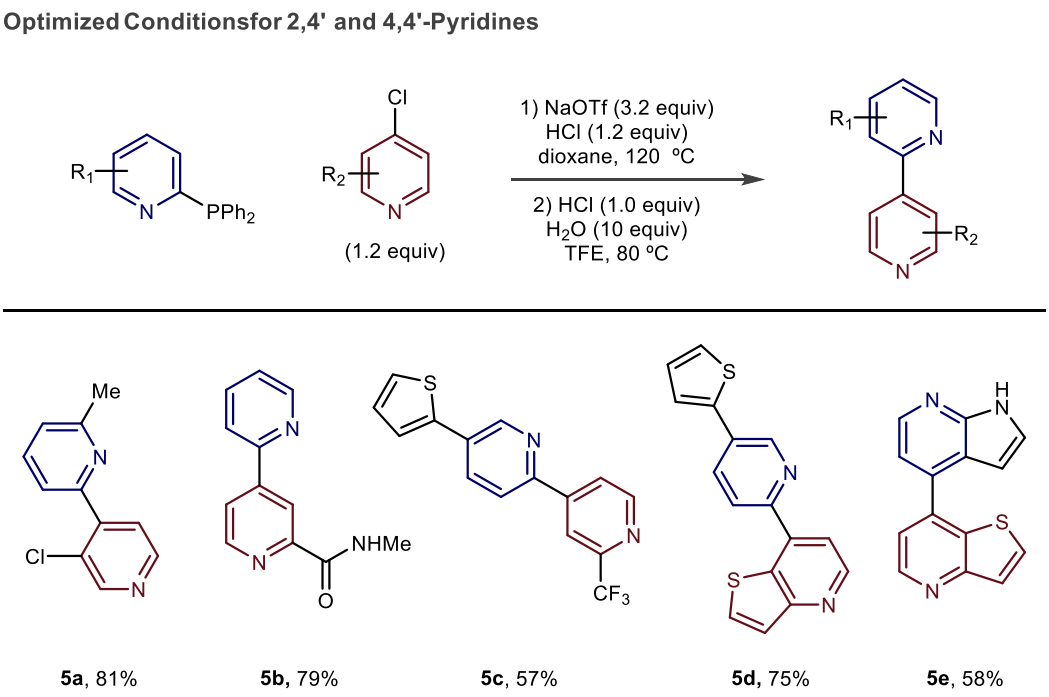


Scheme 4.6: Sequential S_NAr Ligand-Coupling Initial Result

4.3.2 Optimized Conditions for 2,4'- and 4,4'-Bipyridines

The two-stage process involving phosphonium salt formation by an S_NAr reaction followed by ligand-coupling was later optimized by Ben Boyle, a co-worker in the McNally lab. To improve the atom economy of this reaction the pyridyl phosphine was changed to the limiting reagent. In

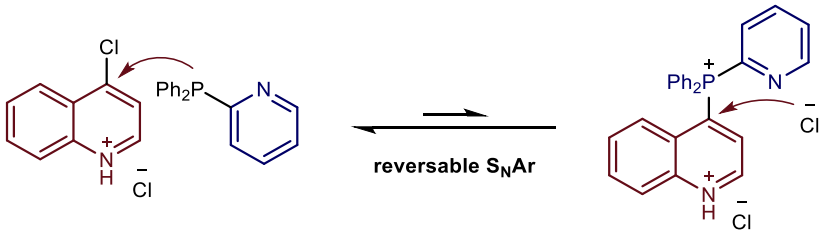
the first stage, ethanol was replaced with 1,4-dioxane, sodium triflate was used as an additive, and the reaction was heated to 120 °C. While ethanol could be used to make the bis-heterobiaryl phosphonium salt at much lower temperatures, the competing ethanolysis posed a problem when more S_NAr active substrates are used. In the second stage HCl, water, and trifluoroethanol (TFE) were added and the reaction was heated to 80 °C. Triflic acid (TfOH) was found to give nearly identical yields to HCl. This set of conditions were found to be optimal for 2,4'- and 4,4'-couplings (**Scheme 4.7**). For 2,4'-couplings it is best to use the 2-pyridyl phosphine as the donor as opposed to using a 4-pyridyl phosphine. Fluoro and bromopyridines can be used as well, but generally, give lower yields of the heterobiaryl product when compared with the chloropyridine.



Scheme 4.7: 2,4'- and 4,4'-Bipyridine Scope

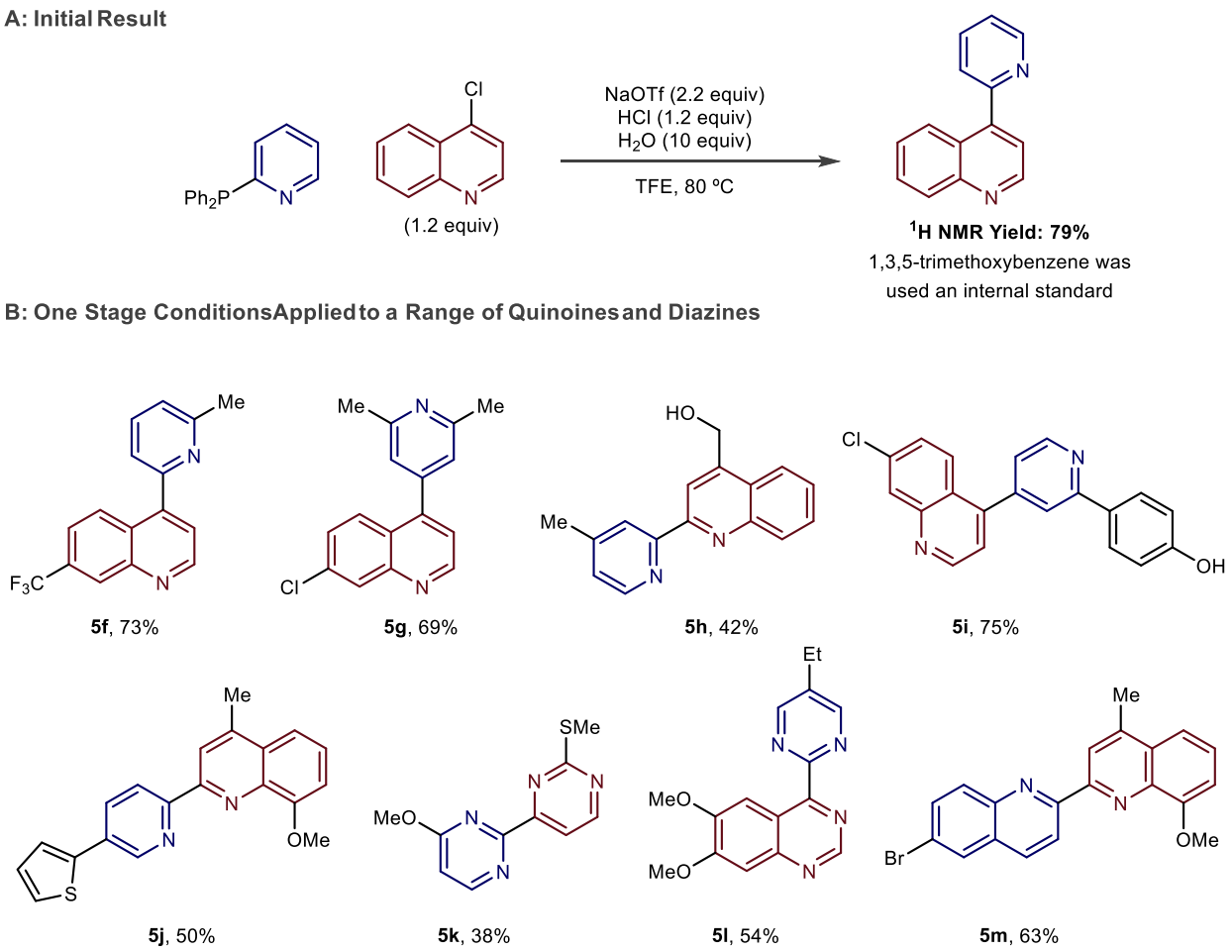
4.3.3 Optimized Conditions for Quinolines and Diazines

The initial set of conditions to make 2,4' and 4,4'-bipyridines failed when applied to chloroquinolines and diazines. It was found that phosphonium salt formation was not going to completion after stage one. This was an unexpected result as chloroquinolines and diazines are significantly more reactive in S_NAr reactions. It was later observed that the reverse reaction, chlorination via an S_NAr process, was occurring and preventing the reaction from going to completion (**Scheme 4.8**).



Scheme 4.8: Quinolines and Diazines Failed to go to Competition in Salt Formation

To solve this problem, we proposed trapping the phosphonium salt *in-situ*. If the nucleophile which initiates ligand-coupling was in the reaction from the start, then it could intercept the phosphonium salt before the reverse reaction could occur. Initially, we used 1.2 equivalents of HCl, 10 equivalents of H_2O, and trifluoroethanol as the solvent. Heating to 80 °C was sufficient to form the phosphonium which was subsequently reacted with H_2O to give the bis-heterobiaryl via ligand-coupling (**Scheme 4.9**). When coupling a pyridine to a quinoline (**5f-j**) it is best to use the quinoline as the acceptor (i.e. the chloroazine) and the pyridine as the donor (i.e. the heteroaryl phosphine). Diazines (**5k and 5l**) were found to work well when paired with other diazines but can also be paired with a pyridine or quinoline based on our previous work.[16] While pyrimidines and quinazolines worked in reasonably yield, pyrazines were either low yielding or did not work at all.



Scheme 4.9: Initial Result and Scope of Quinoline and Diazine Couplings

4.3.4 Optimized Conditions for 2,2'-Bipyridines

The initial set of conditions to make 2,4' and 4,4'-bipyridines failed when applied to synthesize 2,2'-bipyridines as the formation of the phosphonium salt was also not going to completion. The S_NAr reaction was found to be more difficult at the 2-position than at the 4-position and thus a different set of conditions were required (**Table 4.1**). Stage one was optimized to improve phosphonium salt formation and 2,5-chloropyridine and 2-pyridyl phosphine were chosen as coupling partners. Initially, it was found that switching from dioxane to a less polar solvent such as toluene (tol.) or chlorobenzene (PhCl) considerably improved the yield. Triflic

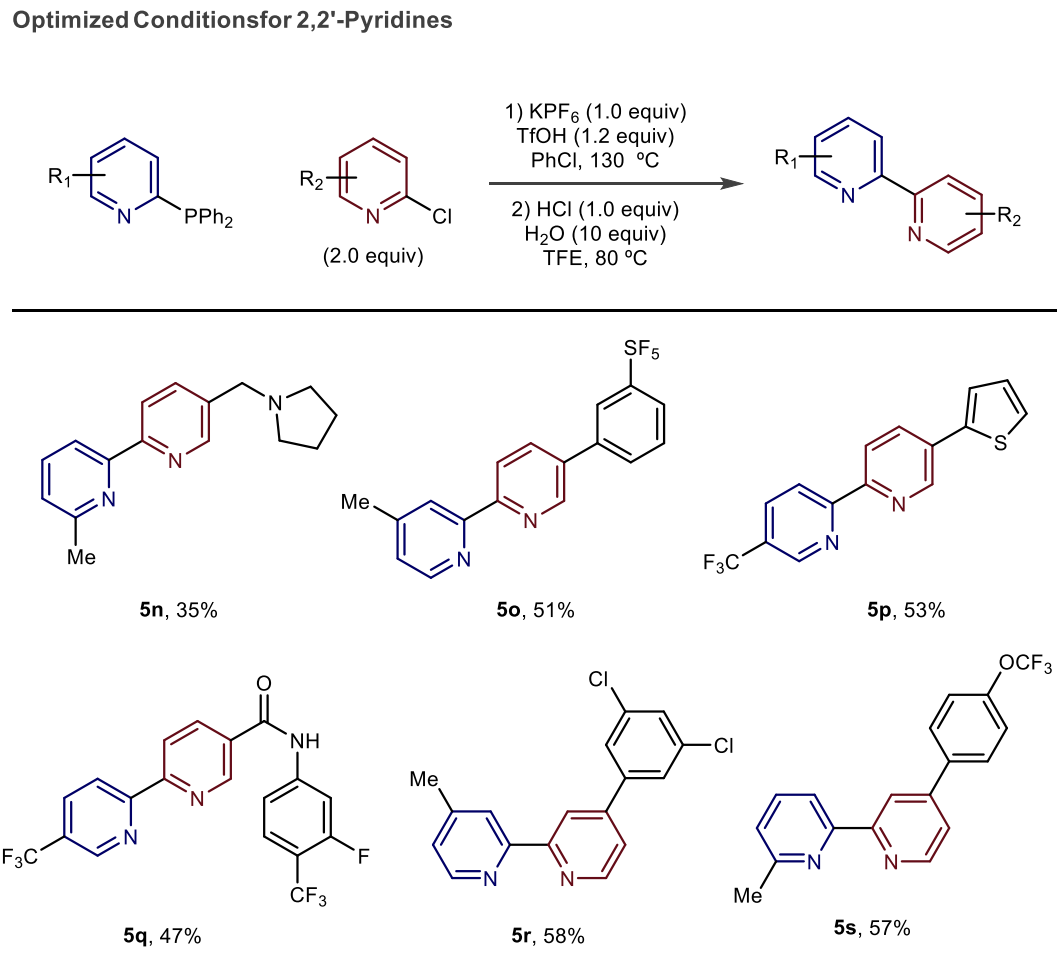
acid performed better than HCl and changing the additive to KPF_6, increased the yield further. Temperature proved to be one of the most important factors; heating to 130 °C gave the best yields, whereas heating to 140 °C would give unwanted side products (**Scheme 4.15**).

Table 4.1: Optimization of Phosphonium Salt for 2,2'-Coupling

Entry	Solvent	Additive	Temp. °C	Conc. (M)	Acid	Yield (%)*
1	dioxane/tol. (1:1)	NaOTf	120	2	HCl	43
2	dioxane/tol. (1:1)	KPF_6	120	2	HCl	49
3	dioxane/tol. (1:1)	NaOTf	120	2	TfOH	42
4	dioxane/tol. (1:1)	none	120	2	TfOH	57
5	dioxane	none	120	2	TfOH	46
6	tol.	none	120	2	TfOH	60
7	tol.	KPF_6	120	2	TfOH	66
8	tol.	none	130	2	TfOH	70
9	PhCl	none	120	2	TfOH	51
10	PhCl	none	130	2	TfOH	67
11	PhCl	none	140	2	TfOH	69†
12	**PhCl**	**KPF_6**	**130**	**2**	**TfOH**	**81**
13	PhCl	KPF_6‡	130	2	TfOH	73
14	PhCl	$NaPF_6$	130	2	TfOH	79
15	PhCl	$LiPF_6$	130	2	TfOH	78

*^{1}H NMR yields shown using triphenylmethane as an internal standard. †Undesired phosphonium salt observed. ‡1.5 equivalents of KPF_6 was used instead of 1.0 equivalents.

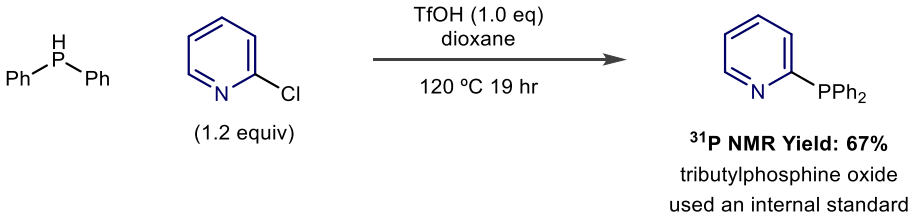
After improving the salt yield in stage one, stage two was found to require no change. This two-stage process was applied to a range of 2-chloropyridines and 2-pyridyl phosphines to make 2,2'-bipyridines (**Scheme 4.10**). Tertiary amines (**5n**), amides (**5q**) and halogens (**5r**) can be tolerated in this process. Other examples feature medically relevant SF_5 (**5o**), CF_3 (**5p**), and OCF_3 (**5e**) groups. It was found that 2,2'-couplings were generally lower yielding (35-58%) than that of 2,4'- or 4,4'-couplings. The reason for this difference is currently being investigated by the McNally and Paton labs.



Scheme 4.10: Scope of 2,2'-Bipyridines

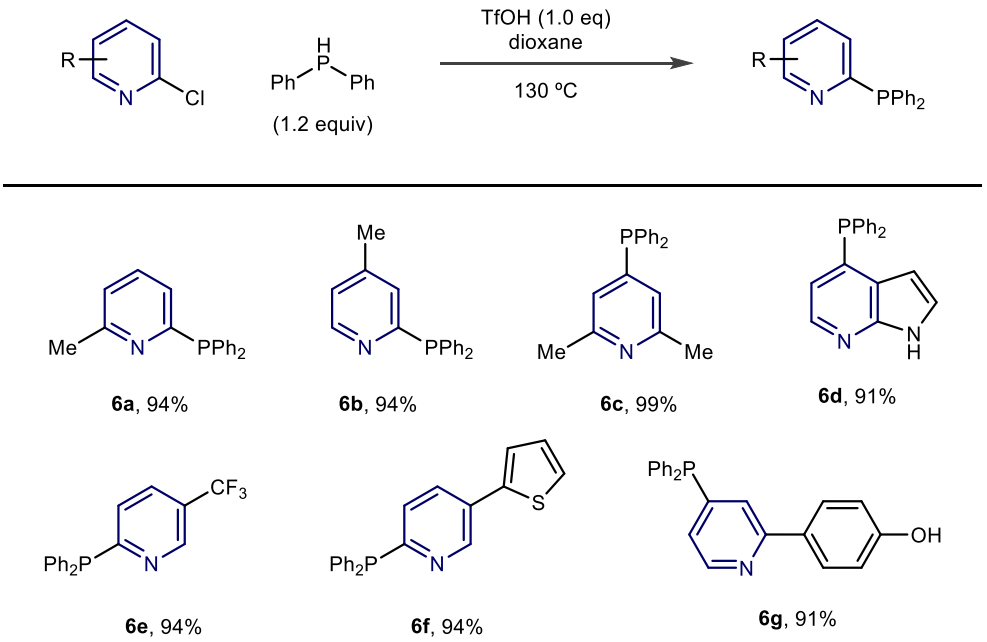
4.3.5 Synthesis of Heteroaryl Phosphines via Acidic S_NAr Conditions

After our initial findings showed that bis-heterobiaryl phosphoniums could be prepared using acidic S_NAr conditions, Ben Boyle discovered that a similar approach could be applied to prepare the heteroaromatic phosphines. It was found that diphenylphosphine could be reacted with 1.2 equivalents of 2-chloropyridine and 1.0 equivalent of triflic acid in dioxane at 120 °C. Triflic acid served to make the 2-chloropyridine more reactive towards the S_NAr process. After 19 hours, 2-pyridyl phosphine was formed in 67% yield (**Scheme 4.11**).



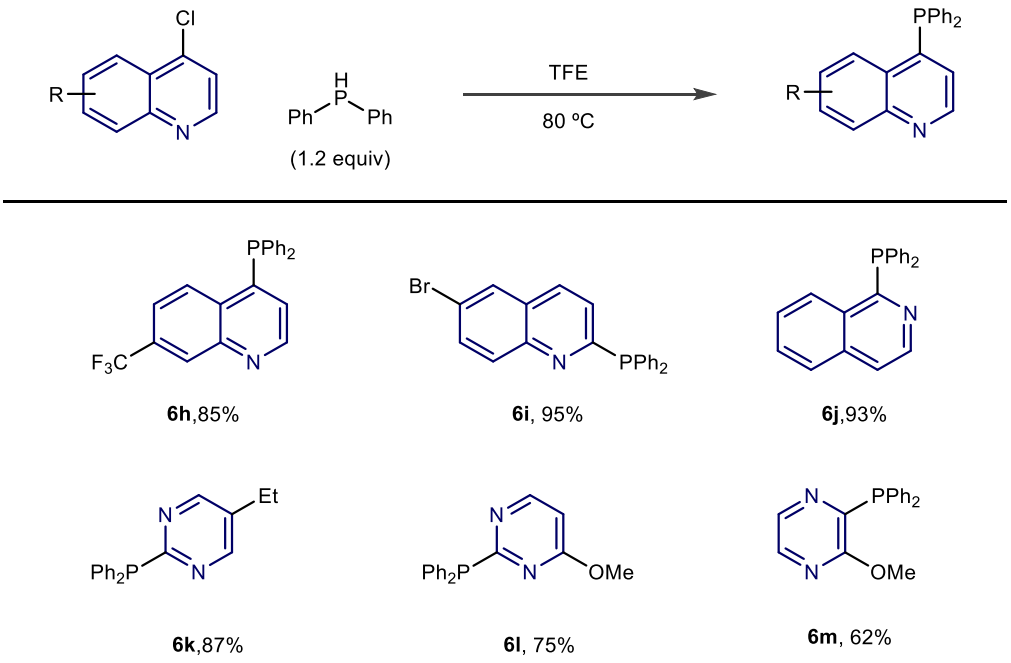
Scheme 4.11: Pyridyl Phosphine Synthesis by S_NAr Initial Result

The reaction was later optimized to be more general and operationally simpler. The first change was making the chloroazine the limiting reagent as separating the excess chloroazine from the heteroaryl phosphine proved difficult. Changing the solvent to chlorobenzene and increasing the temperature to 130 °C significantly improved the yields. The optimized conditions and scope of the pyridyl phosphines can be seen in **Scheme 4.12**. The phosphines are typically benchtop stable powders but for long-term storage, the phosphines can be kept in a –20 °C fridge to slow undesired oxidation.



Scheme 4.12: Scope of Pyridyl Phosphines

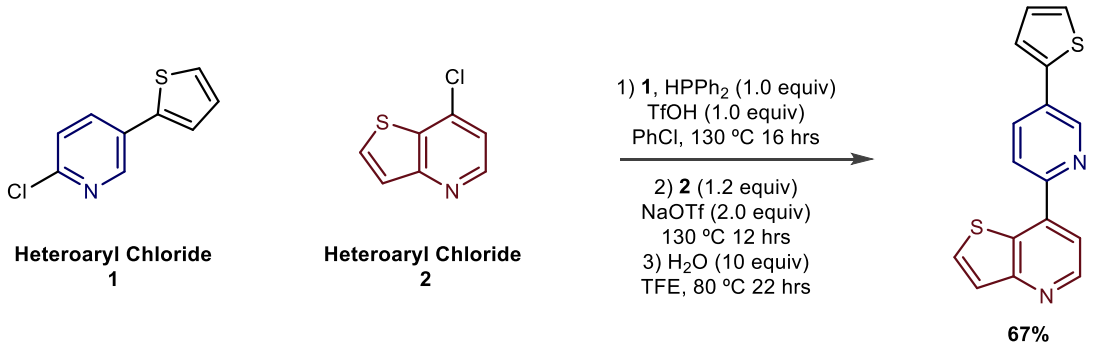
For the more electron-deficient azines such as quinolines and diazines, milder conditions were used. Heating the chloroazine with 1.2 equivalents of diphenylphosphine in trifluoroethanol at 80 °C was sufficient to get high yields. Acid was not required in these examples and the harsher conditions would lead to dehalogenation of the starting material. The optimized conditions and scope of these phosphines can be seen in **Scheme 4.13**.



Scheme 4.13: Scope of Heteroaromatic Phosphines (Quinolines and Diazines)

4.3.6 One-Pot Conditions for Bis-Heterobiaryl Synthesis

Ben Boyle found that the bis-heterobiaryl could be formed in a one-pot reaction from the respective chloroazines. Heteroaryl chloride **1** was reacted with diphenylphosphine and triflic acid at 130 °C for 16 hours (**Scheme 4.14**). Heteroaryl chloride **2** was then added along with sodium triflate and the reaction was heated to 130 °C for 12 hours. Lastly, 10 equivalents of water and TFE were added. Heating to 80 °C for 22 hours lead to a 2,4'-bipyridine in 67% yield. The other sets of conditions for quinolines, diazines, and 2,2'-bipyridines could be modified to be a one-pot process.



Scheme 4.14: One-Pot Synthesis of 2,4'-Bipyridine from Chloropyridines

4.3.7 Problematic Substrates and Undesired Pathways

While this process to make heterobiaryls could be applied to a range of pyridines and other azines it is inherently limited in that we must carry out an S_NAr reaction to make the phosphines and phosphoniums. Only the 2- and 4-halopyridines are suitable for this process while the 3-halopyridines are unreactive under these conditions. Chloropyridines with electron-donating groups show poor reactivity as well (**Figure 4.2**). Pyridines with multiple halogens at S_NAr active positions are not tolerated due to poor selectivity and over-reactivity. Both 2-chloro-5-fluoropyridine and 2-chloro-3-fluoropyridine performed poorly when making the phosphine due to poor reactivity and oxidation of the resulting phosphine, respectively. Bromo and iodo atoms at the 3- or 5-positions on pyridine were avoided due to dehalogenation as noted in the previous chapter. Similarly, alkoxyl groups at the 2-positon were avoided due to dealkylation.

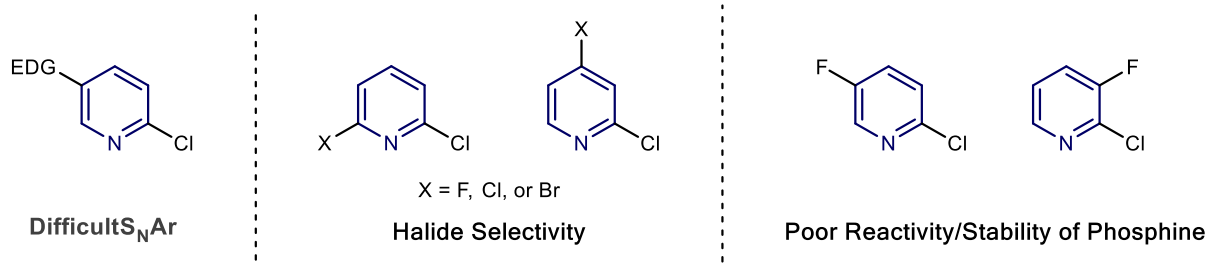


Figure 4.2: Difficult Chloropyridines for Phosphine and Phosphonium Salt Formation

In some examples the phosphine and subsequent phosphonium salt formation would succeed, but ligand-coupling would fail (**Figure 4.3**). This was the case when trying to carry a 4,4'-coupling between two quinolines. After salt formation, no ligand coupling products were observed even after heating to elevated temperatures. A similar result was observed when making a 2,2'-bipyridine when one of the pyridines featured a 2- or 4-amino group.

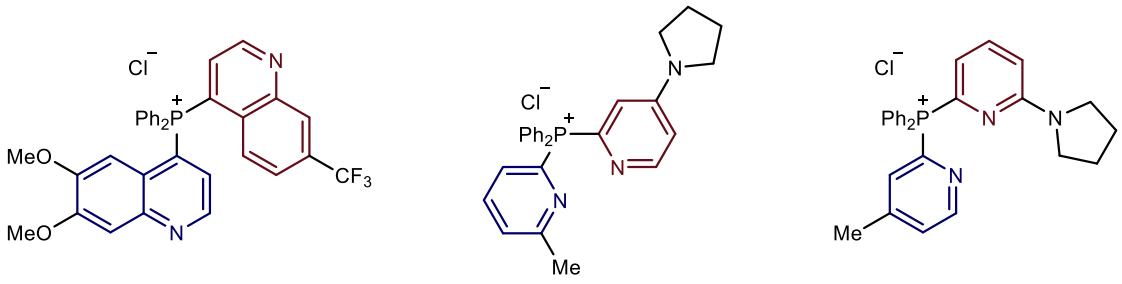
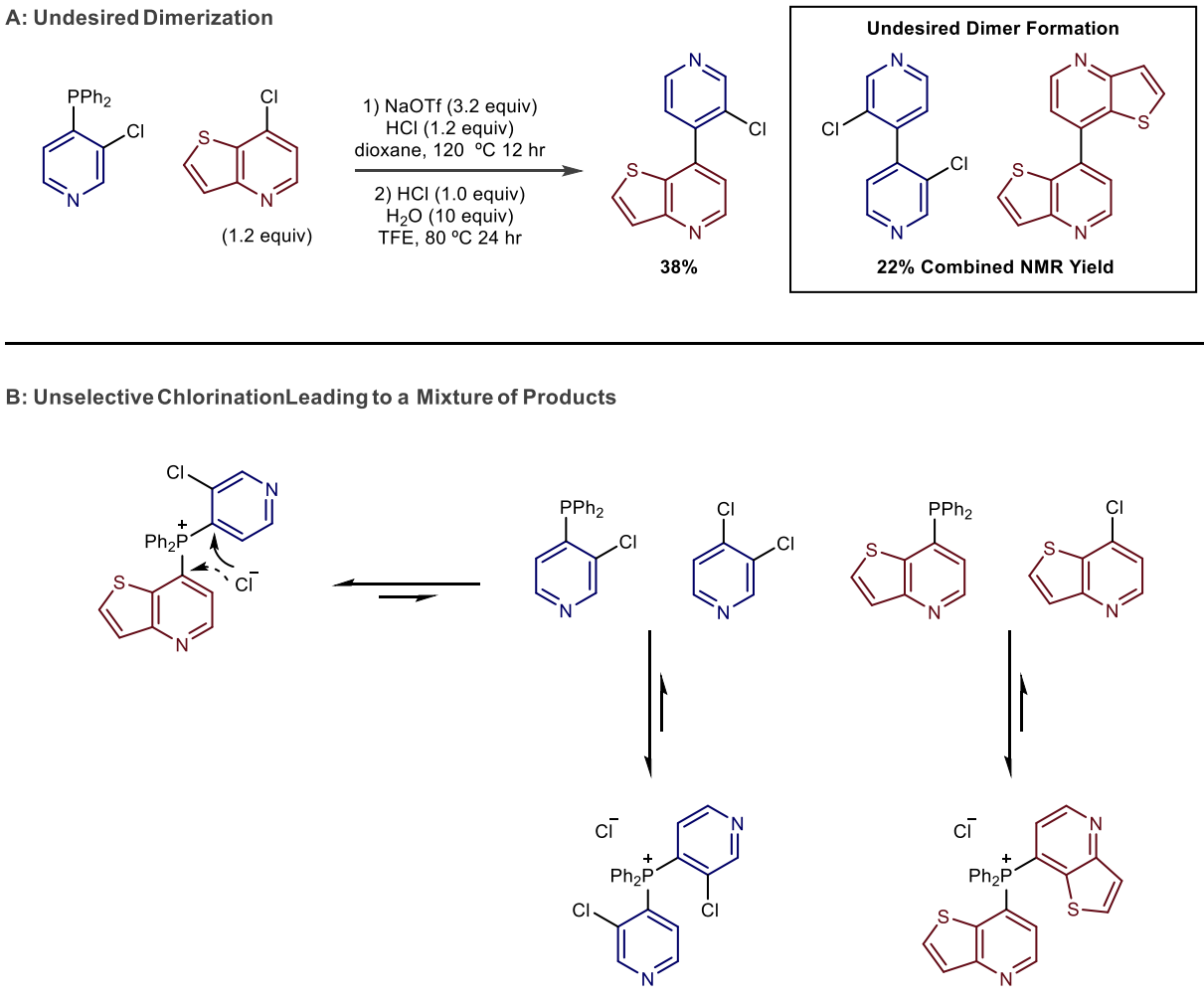


Figure 4.3: Examples Where Ligand-Coupling Failed

In a few rare cases, we would observe a chloro-phosphine metastasis between the two azines. In this undesired process the phosphonium salt forms but then subsequently reacts with a chloride ion via an S_NAr reaction. If the chlorination is unselective, this leads to a mixture of two different heteroaryl chlorides and two different heteroaryl phosphines. From this mixture, three different phosphonium salts could form leading to three different bis-heterobiaryl products after ligand-coupling. An example of this process can be seen in **Scheme 4.15.**



Scheme 4.15: **(A)** Undesired Dimerization Observed Experimentally. **(B)** Formation of Three Different Phosphonium Salts via Chlorination

4.4 Comparisons with Other Cross-Coupling Methods

4.4.1 Improvements to Previous Ligand-Coupling Method

When compared with our previous method[16] to make bis-heterobiaryls, the tandem S_NAr-ligand-coupling approach has some clear advantages (**Figure 4.3**). The ability to make the bis-heterobiaryl phosphonium salt from the C–H bond of the azines using triflyl activation is desirable, but the high selectivity of the reaction for the 4-position of pyridine limits the different types of

couplings which can be achieved. From the C–Cl bond, you can access phosphoniums which cannot be made using the previous method. For example, to carry out a 2,2'-coupling this would require the 4-position to be blocked for each pyridine to access the 2-position C–H bonds. Using the tandem S_NAr-ligand-coupling approach, a 2,2'-bipyridine can be synthesized from two different chloropyridines without concerns of selectivity.

Another advantage of this method is that it can tolerate substitution patterns and functionality that were problematic in our previous strategy. 2,6-Disubstituted and 2-trifluoromethylpyridines presented issues for triflyl activation but do not interfere with the S_NAr reaction when making the phosphonium salt. Functional groups such as alkyl amides, alcohols, and phenols react with triflic anhydride and thus were previously avoided. All these functional groups are tolerated in the S_NAr reaction and the subsequent ligand-coupling reaction.

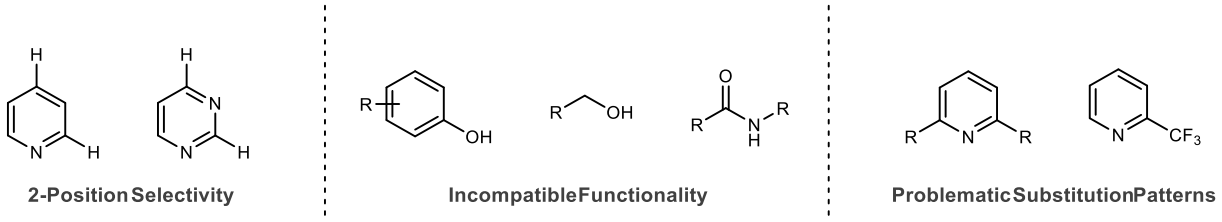
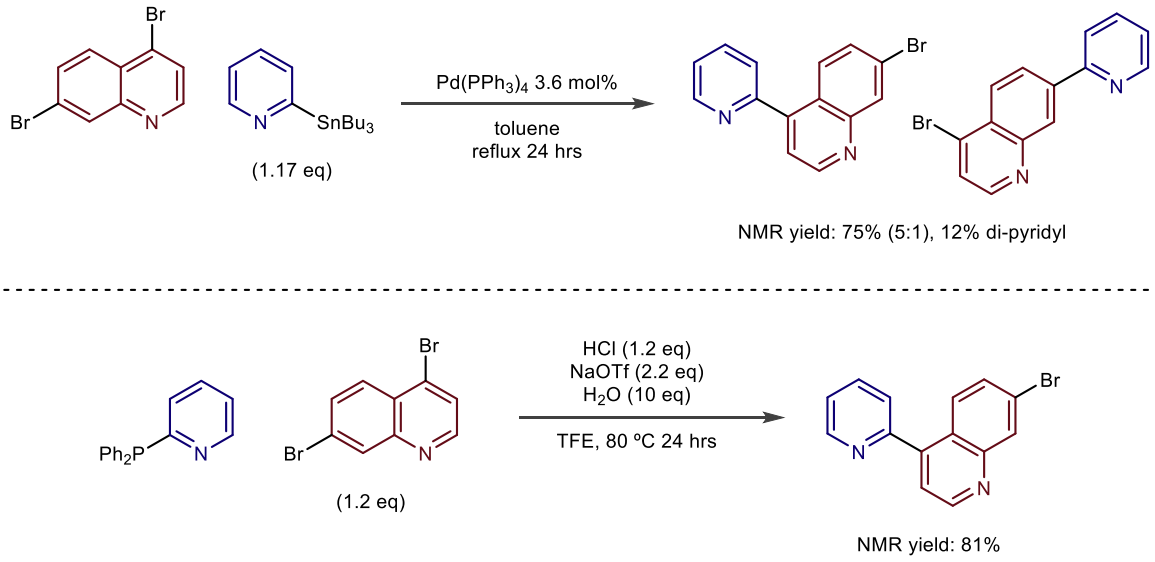


Figure 4.3: Issues which are Addressed using the Tandem S_NAr-Ligand-Coupling Approach

4.4.2 Comparison with Metal-Catalyzed Cross-Coupling

An important consideration in cross-coupling is halide selectivity in structures featuring two or more halogens. In many examples, the metal will not discriminate, and this will lead to a mixture of products. The tandem S_NAr-ligand-coupling approach avoids this issue as it is selective for the halide at the most S_NAr active position. To demonstrate this utility, we carried out a comparison study of the two methods using 4,7-dibromoquinoline as a model substrate

(**Scheme 4.16**). Using 2-pyridylstannane and standard conditions for a bis-heterobiaryl Stille coupling we observed a mixture of products. When the tandem S_NAr-ligand-coupling approach was used we observed exclusive reactivity at the 4-position.



Scheme 4.16: Comparison Study Between Cross-Coupling Strategies

4.5 Conclusion

The tandem S_NAr-ligand-coupling approach provides a new way to access bis-heterobiaryls that are difficult to prepare using our previous method or through metal-catalyzed cross-couplings. Specifically, the 2,2'-bipyridine motif is an important structural feature in various areas of chemistry and being able to easily access these compounds is an advancement to current synthetic methods. This method is operationally simple and can be applied to a range of commercially available chloroazines.

REFERENCES

(1) Boyle, B. T.; Hilton, M. C.; McNally, A. *ChemRxiv Prepr.* **2019**.

(2) Roecker, A. J.; Mercer, S. P.; Schreier, J. D.; Cox, C. D.; Fraley, M. E.; Steen, J. T.; Lemaire, W.; Bruno, J. G.; Harrell, M. C.; Garson, S. L.; et al. *ChemMedChem* **2014**, 9, 311.

(3) Tre´court, F.; Gervais, B.; Mallet, M.; Que´guiner, G. *J. Org. Chem.* **1996**, 61, 1673.

(4) Watanabe, Y.; Sasabe, H.; Yokoyama, D.; Beppu, T.; Katagiri, H.; Kido, J.. *J. Mater. Chem. C* **2016**, 4, 3699.

(5) Schubert, U.; Eschbaumer, C. *Angew. Chem. Int. Ed.* **2002**, 41, 2892.

(6) Newkome, G. R.; Patri, A. K.; Holder, E.; Schubert, U. S. *Eur. J. Org. Chem.* **2004**, 235.

(7) Kaes, C.; Katz, A.; Hosseini, M. W. *Chem. Rev.* **2000**, 100, 3553.

(8) Cox, P. A.; Reid, M.; Leach, A. G.; Campbell, A. D.; King, E. J.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2017**, 139, 13156.

(9) Cox, P. A.; Leach, A. G.; Campbell, A. D.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2016**, 138, 9145.

(10) Blakemore, D. C.; Doyle, P. M.; Fobian, Y. M. *Synthetic Methods in Drug Discovery: Volume 1*; Royal Society of Chemistry, 2016.

(11) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, 131, 6961.

(12) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, 68, 4302.

(13) Ren, W.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Tetrahedron* **2012**, 68, 1351.

(14) Markovic, T.; Rocke, B. N.; Blakemore, D. C.; Mascitti, V.; Willis, M. C. *Chem. Sci.* **2017**, 8, 4437.

(15) Mecˇ iarova, M. ria; Toma, S. tefan; Loupy, A. *PHOSPHORUS SULFUR* **2008**, 183, 21.

(16) Hilton, M. C.; Zhang, X.; Boyle, B. T.; Alegre-Requena, J. V.; Paton, R. S.; McNally, A. *Science* **2018**, 362, 799.

SUMMARY

The work described in this dissertation shows the development and application of heterocyclic phosphonium salts in the selective functionalization of pyridines and other azines. The abundance of pyridines in pharmaceuticals and the difficulty in selectively functionalizing these structures make this research appealing to the field of medicinal chemistry. The phosphonium is installed selectively to the 4-position of pyridine and subsequent transformations can be carried out on this group. We were able to show that carbon-heteroatom bonds could easily be accessed by reacting phosphonium salts with various nucleophiles such alkoxides, thiolates, and azides. This method provides an alternative approach to S_NAr and metal-catalyzed processes which are limited by the requirement of a heteroaryl halide which can be difficult to synthesize.

Additionally, this dissertation describes the development of a new approach to synthesize bis-heterobiaryls using phosphorus ligand-coupling. Through the preparation of bis-heterobiaryl phosphonium salts, we could selectively couple two different azines by reacting them with acid in either alcohol or water. Importantly, this approach addresses some of the problems associated with metal catalysts and coupling partners required in metal-catalyzed cross-couplings. While phosphorus ligand-coupling has been known process, it has seen little application in synthesis. Our method provides a convenient strategy to access bis-heterobiaryls which are commonly found in various areas of chemistry.

APPENDIX ONE

Heteroaryl Ether Synthesis using Heterocyclic Phosphonium Salts: Experimental

(Combined Work of Ryan Dolewski and Michael Hilton)

A 1.1 General Methods and Materials

PPh_3 (99%) was purchased from Oakwood Chemical and is most effective when crushed to a powder before use. Tf_2O (99%) was purchased from Oakwood Chemical and used without further purification but was routinely stored in a –20 ºC fridge. NEt_3 and DBU were distilled before use. NaH (60% in mineral oil) was purchased from Sigma Aldrich and was typically distributed into vials and stored in a desiccator. All reactions were run under a nitrogen atmosphere unless otherwise noted.

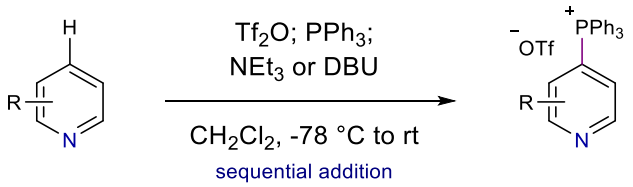
A 1.2 Instrumentation

^1H NMR spectra were recorded using a Varian 400 MR spectrometer (400 MHz) or an Agilent Inova 400 (400 MHz) spectrometer. The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: $CDCl_3$ (7.26 ppm), $(CD_3)_2SO$ (2.50 ppm), or CD_3OD (3.31 ppm). Coupling constants (*J*) were reported in Hertz (Hz) and the multiplicity was reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. ^{13}C NMR spectra were recorded using a Bruker Ultrashield–400, a Varian 400 MR or an Agilent Inova 400 spectrometer. The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: $CDCl_3$ (77.00 ppm), $(CD_3)_2SO$ (39.51

ppm), or CD_3OD (49.00 ppm). Low–resolution mass spectra were recorded on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared spectra were recorded on a Bruker Tensor 27 FT–IR spectrometer with absorptions reported in wavenumbers (cm^{-1}). Melting points were recorded using a Büchi B–450 melting point apparatus.

A 1.3. General Procedures

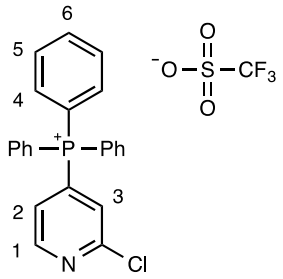
A 1.3.1 General Procedure A (Preparation of Heterocyclic Phosphonium Salts)



An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before PPh_3 (1.1 equiv) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 minutes at –78 ºC. The stated organic base (NEt_3 or DBU, 1.0 equiv) was added dropwise via syringe, the cooling bath was removed, and the reaction was allowed to warm to room temperature while stirring (approximately 15-30 minutes). The reaction mixture was quenched with H_2O (approximately the same volume as CH_2Cl_2) and the mixture was transferred to a separatory funnel. The mixture was diluted CH_2Cl_2 and the resulting organic layer was washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to approximately 2-10 mL (depending on the scale of the reaction). An excess of chilled Et_2O (0 ºC) was added to the concentrated solution that was

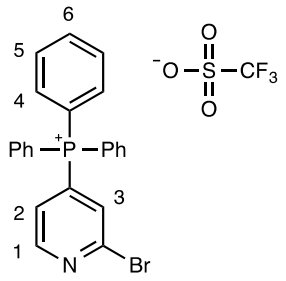
then placed in a –20 ºC refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 ºC) and dried *in vacuo* to provide the pure phosphonium salt.

(2-Chloropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2a)



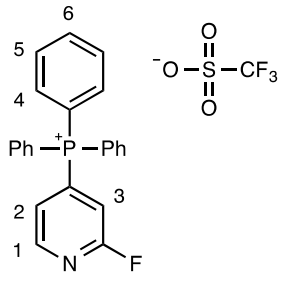
Prepared according to general procedure A using 2-chloropyridine (473 μL, 5.00 mmol), Tf_2O (845 μL, 5.00 mmol), PPh_3 (1.44 g, 5.50 mmol), NEt_3 (697 μL, 5.00 mmol) and CH_2Cl_2 (50 mL). After the purification procedure, the title compound was isolated as a white solid (2.14 g, 4.08 mmol, 82% yield). mp 158-160 ºC; IR ν_{max}/cm^{-1} (film): 3087, 3061, 3028, 1459, 1264, 1137, 1110, 1031, 749, 726, 634; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.82 (1H, app t, J = 5.1 Hz, H_1), 7.98-7.89 (3H, m, H_6), 7.86-7.77 (6H, m, H_5), 7.75-7.62 (7H, m, H_2 and H_4), 7.40 (1H, d, J = 13.2 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.38 (d, J = 15.1 Hz), 152.31 (d, J = 11.3 Hz), 136.41 (d, J = 3.0 Hz), 134.49 (d, J = 10.4 Hz), 132.01 (d, J = 83.2 Hz), 131.11 (d, J = 13.0 Hz), 127.41 (d, J = 9.5 Hz), 126.28 (d, J = 8.4 Hz), 120.72 (q, J = 320.4 Hz), 115.02 (d, J = 90.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.19; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.27; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 374.1, $C_{23}H_{18}ClNP^+$ requires 374.1.

(2-Bromopyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2b)



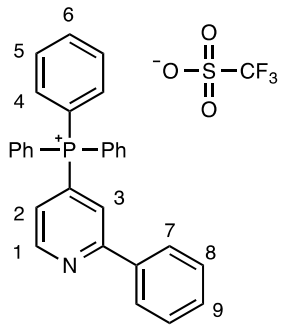
Prepared according to general procedure A using 2-bromopyridine (954 μL, 10.00 mmol), Tf_2O (1.69 mL, 10.00 mmol), PPh_3 (2.89 g, 11.00 mmol), DBU (1.52 mL, 10.00 mmol) and CH_2Cl_2 (100 mL). After the purification procedure, the title compound was isolated as a white solid (4.84 g, 8.52 mmol, 85% yield). mp 129-136 ºC; IR ν_{max}/cm^{-1} (film): 3099, 3059, 3027, 2996, 1264, 1136, 1109, 1030, 634; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, app t, J = 5.1 Hz, H_1), 7.99-7.89 (3H, m, H_6), 7.87-7.73 (7H, m, H_2 and H_5), 7.72-7.60 (6H, m, H_4), 7.54 (1H, d, J = 12.9 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.63 (d, J = 10.8 Hz), 143.77 (d, J = 14.0 Hz), 136.15 (d, J = 3.1 Hz), 134.47 (d, J = 10.6 Hz), 131.67 (d, J = 82.9 Hz), 131.11 (d, J = 13.2 Hz), 130.81 (d, J = 9.2 Hz), 126.58 (d, J = 8.3 Hz), 120.71 (d, J = 320.9 Hz), 115.01 (d, J = 89.7 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.19; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.00; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 418.1, $C_{23}H_{18}BrNP^+$ requires 418.0.

(2-Fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2c)



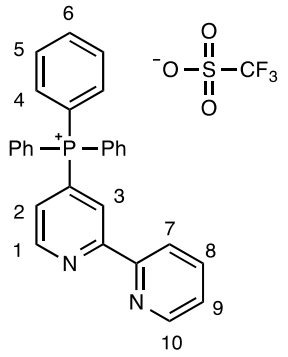
Prepared according to general procedure A using 2-fluoropyridine (859 μL, 10.00 mmol), Tf_2O (1.69 mL, 10.00 mmol), PPh_3 (2.89 g, 11.00 mmol), DBU (1.52 mL, 10.00 mmol) and CH_2Cl_2 (100 mL). After the purification procedure, the title compound was isolated as a white solid (3.96 g, 7.80 mmol, 79% yield). mp 192-196 ºC; IR ν_{max}/cm^{-1} (film): 3087, 3064, 1586, 1437, 1388, 1262, 1227, 1142, 1108, 1031, 726, 718, 687, 634; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.67 (1H, app t, J = 5.3 Hz, H_1), 7.99-7.88 (3H, m, H_6), 7.87-7.75 (6H, m, H_5), 7.74-7.60 (7H, m, H_2 and H_4), 7.10 (1H, d, J = 13.4 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.28 (dd, J = 245.4, 16.9 Hz), 150.63 (dd, J = 13.7, 12.7 Hz), 136.09 (d, J = 3.2 Hz), 134. 21 (d, J = 10.7 Hz), 133.95 (dd, J = 84.4, 6.6 Hz), 130.81 (d, J = 13.8 Hz), 125.18 (dd, J = 8.2, 5.1 Hz), 122.44 (q, J = 321.6 Hz), 114.81 (d, J = 90.1 Hz), 114.19 (dd, J = 40.3, 10.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -61.56 (d, J = 10.3 Hz), -78.20; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.15, (d, J = 9.9 Hz); *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 358.1, $C_{23}H_{18}FNP^+$ requires 358.1.

Triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (2d)



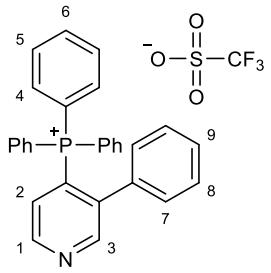
Prepared according to general procedure A using 2-phenylpyridine (2.57 mL, 18.00 mmol), Tf_2O (3.04 mL, 18.00 mmol), PPh_3 (5.19 g, 19.8 mmol), NEt_3 (2.51 mL, 18.00 mmol) and CH_2Cl_2 (180 mL). After the purification procedure, the title compound was isolated as a white solid (8.53 g, 15.08 mmol, 84% yield). mp 169–171 ºC; IR ν_{max}/cm^{-1} (film): 3087, 3066, 3011, 1584, 1570, 1471, 1439, 1374, 1079, 997, 751; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.01 (1H, app t, J = 5.1 Hz, H_1), 7.93–7.54 (18H, m, H_3, H_4, H_5, H_6, and H_7), 7.50 (1H, ddd, J = 17.8, 5.1, 1.1 Hz, H_2), 7.42–7.36 (3H, m, H_8 and H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.09 (d, J = 9.9 Hz), 151.63 (d, J = 10.7 Hz), 136.74 (d, J = 1.5 Hz), 136.14 (d, J = 3.2 Hz), 134.30 (d, J = 9.8 Hz), 130.91 (d, J = 13.0 Hz), 130.35, 129.23 (d, J = 84.1 Hz), 128.98, 127.00, 125.25 (d, J = 7.8 Hz), 123.08, (d, J = 8.4 Hz), 120.68 (q, J = 321.1 Hz), 115.49 (d, J = 89.1 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.7; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 416.2, $C_{29}H_{23}NP^+$ requires 416.2.

[2,2'-Bipyridin]-4-yltriphenylphosphonium trifluoromethanesulfonate (2e)



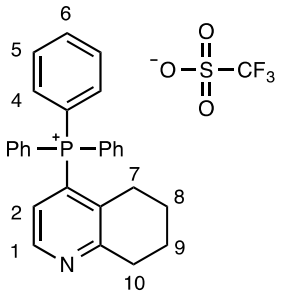
Prepared according to general procedure A using 2,2'-bipyridine (929 mg, 5.95 mmol), Tf_2O (1.00 mL, 5.95 mmol), PPh_3 (1.73 g, 6.55 mmol), NEt_3 (830 μL, 5.99 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a white solid (2.92 g, 5.15 mmol, 87% yield). mp 179-182 ºC; IR ν_{max}/cm^{-1} (film): 3060, 3014, 1576, 1438, 1261, 1142, 1106, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.06 (1H, app t, J = 5.1 Hz, H_1), 8.65 (1H, d, J = 13.8 Hz, H_3), 8.55 (1H, d, J = 4.4 Hz, H_{10}), 8.46 (1H, d, J = 7.9 Hz, H_7), 7.96-7.88 (3H, m, H_6), 7.87-7.74 (7H, m, H_5 and H_8), 7.72-7.55 (7H, m, H_2 and H_4), 7.35 (1H, dd, J = 7.7, 4.5 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.80 (d, J = 9.9 Hz), 153.36 (d, J = 2.3 Hz), 151.37 (d, J = 10.7 Hz), 149.34, 137.34, 136.17 (d, J = 3.1 Hz), 134.42 (d, J = 9.9 Hz), 130.97 (d, J = 13.0 Hz), 129.29 (d, J = 83.9 Hz), 126.91 (d, J = 8.4 Hz), 125.08, 123.89 (d, J = 9.2 Hz), 121.65, 120.80 (q, J = 321.2 Hz), 115.75 (d, J = 89.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.10; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.64; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 417.2, $C_{28}H_{22}N_2P^+$ requires 417.2.

Triphenyl(3-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (2f)



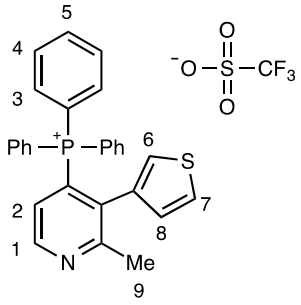
Prepared according to general procedure A (except that the stirring time after addition of PPh_3 was 1 hour instead of 30 minutes) using 3-phenylpyridine (400 mg, 2.58 mmol), Tf_2O (435 μL, 2.58 mmol), PPh_3 (744 mg, 2.84 mmol), DBU (285 μL, 2.58 mmol) and CH_2Cl_2 (26 mL). After the purification procedure, the title compound was isolated as a white solid (1.05 g, 1.86 mmol, 72% yield). mp 185-188 ºC; IR ν_{max}/cm^{-1} (film): 3032, 2980, 2948, 1518, 1407, 1292, 1249, 1186, 825; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.95 (1H, app t, J = 4.7 Hz, H_1), 8.74 (1H, d, J = 6.8 Hz, H_3), 7.85-7.73 (3H, m, H_6), 7.73-7.40 (13H, m, H_2, H_4, and H_5), 7.11 (1H, t, J = 7.6 Hz, H_9), 6.91 (2H, app t, J = 7.6 Hz, H_8), 6.71 (2H, d, J = 7.5 Hz, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.63 (d, J = 8.0 Hz), 149.97 (d, J = 10.4 Hz), 141.68 (d, J = 7.3 Hz), 135.43 (d, J = 3.0 Hz), 134.41 (d, J = 4.5 Hz), 134.18 (d, J = 10.3 Hz), 130.59 (d, J = 13.0 Hz), 129.21, 128.89, 128.30, 128.20, 126.35 (d, J = 83.4 Hz), 120.82 (q, J = 321.2 Hz), 116.89 (d, J = 89.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: −77.68; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.73; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 416.2, $C_{29}H_{23}NP^+$ requires 416.2.

Triphenyl(5,6,7,8-tetrahydroquinolin-4-yl)phosphonium trifluoromethanesulfonate (2g)



Prepared according to general procedure A (except the product suspension was placed in a –20 ºC refrigerator for approximately 12 hours instead of 1 hour) using 5,6,7,8-tetrahydroquinoline (773 μL, 5.95 mmol), Tf_2O (1.00 mL, 5.95 mmol), PPh_3 (1.73 g, 6.55 mmol), DBU (890 μL, 5.95 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a pale tan solid (2.24 g, 4.13 mmol, 69% yield). mp 248-251 ºC; IR ν_{max}/cm^{-1} (film): 3019, 2954, 1442, 1259, 1144, 1029; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.74 (1H, app t, J = 5.1 Hz, H_1), 8.07-7.93 (3H, m, H_6), 7.92-7.71 (12H, m, H_4 and H_5), 6.94 (1H, dd, J = 15.3, 5.1 Hz, H_2), 3.12-2.97 (2H, m, H_{10}), 2.21-2.04 (2H, m, H_7), 1.84-1.71(2H, m, H_9), 1.60-1.44 (2H, m, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.25 (d, J = 8.4 Hz), 148.20 (d, J = 11.4 Hz), 135.48 (d, J = 7.6 Hz), 135.27 (d, J = 3.1 Hz), 134.06 (d, J = 10.7 Hz), 130.50 (d, J = 13.0 Hz), 126.18 (d, J = 9.9 Hz), 125.51 (d, J = 82.4 Hz), 120.40 (q, J = 322.0 Hz), 116.34 (d, J = 87.7 Hz), 32.01 (d, J = 2.3 Hz), 29.66 (d, J = 5.3 Hz), 21.03, 20.54; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -77.75; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.85; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 394.2, $C_{27}H_{25}NP^+$ requires 394.2.

(2-Methyl-3-(thiophen-3-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2h)

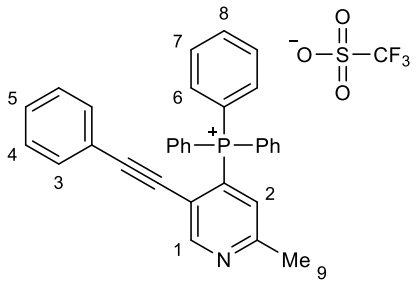


Prepared according to general procedure A (except that the stirring time after addition of PPh_3 was 1 hour instead of 30 minutes and an additional hour of stirring at room temperature after addition of DBU) using 2-methyl-3-(thiophen-3-yl)pyridine (518 mg, 3.00 mmol), Tf_2O (500 μL, 3.00 mmol), PPh_3 (775 mg, 3.30 mmol), DBU (448 μL, 3.00 mmol) and CH_2Cl_2 (30 mL). After the purification procedure,[1] the title compound was isolated as a tan solid (1.04 g, 1.78 mmol, 59% yield). mp 182-185 ºC; IR ν_{max}/cm^{-1} (film): 3112, 3072, 2976, 1272, 1262, 1168, 1153, 1027, 632; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.82 (1H, app t, J = 5.0 Hz, H_1), 7.86-7.77 (3H, m, H_5), 7.75-7.65 (6H, m, H_4), 7.63-7.52 (6H, m, H_3), 7.28-7.18 (1H, m, H_2), 6.85 (1H, dd, J = 5.1, 2.9 Hz, H_8), 6.58 (1H, dd, J = 2.9, 1.1 Hz, H_6), 6.20 (1H, dd, J = 5.1, 1.2 Hz, H_7), 2.31 (3H, s, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.95 (d, J = 8.1 Hz), 149.44 (d, J = 10.8 Hz), 135.84 (d, J = 7.6 Hz), 135.21 (d, J = 3.0 Hz), 134.56 (d, J = 5.3 Hz), 133.80 (d, J = 9.9 Hz), 130.49 (d, J = 12.9 Hz), 128.05, 127.68 (d, J = 84.8 Hz), 126.48, 125.97, 125.86 (d, J = 9.6 Hz), 120.69 (q, J = 320.9 Hz), 117.16 (d, J =

[1] The concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of chilled Et_2O (0 °C) instead of the order of addition in General Procedure A. The mixture was then placed in a -20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled Et_2O (0 °C). The solid was redissolved in approximately 10 mL of CH_2Cl_2 and was precipitated a second time via dropwise addition to an excess of chilled Et_2O (0 °C). The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt.

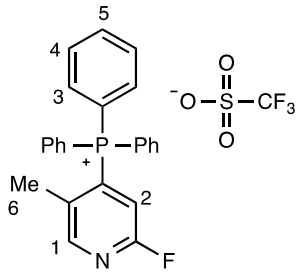
89.6 Hz), 23.54 (d, J = 2.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.03; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.38; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 436.1, $C_{28}H_{23}NPS^+$ requires 436.1.

(2-Methyl-5-(phenylethynyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2i)



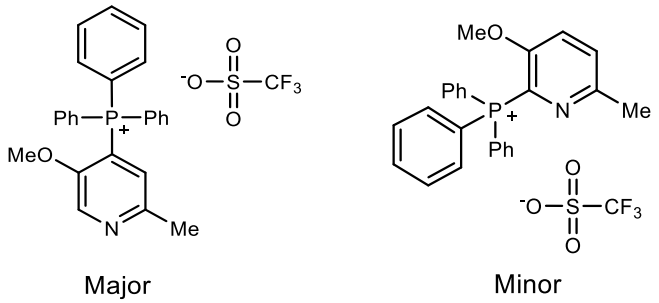
Prepared according to general procedure A using 2-methyl-5-(phenylethynyl)pyridine (860 mg, 4.45 mmol), Tf_2O (749 μL, 4.45 mmol), PPh_3 (1.29 g, 4.90 mmol), DBU (619 mL, 4.45 mmol) and CH_2Cl_2 (40 mL). After the purification procedure, the title compound was isolated as an off-white solid (1.60 g, 2.65 mmol, 60% yield). mp 188–190 ºC; IR ν_{max}/cm^{-1} (film): 3098, 2214, 1584, 1462, 1260, 1028, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, d, J = 2.8 Hz, H_1), 7.86 (3H, m, H_8), 7.80–7.68 (13H, m, H_7, H_6, and H_5), 7.17 (2H, app t, J = 7.7 Hz, H_4), 7.09 (1H, d, J = 15.1 Hz, H_2), 6.66 (2H, d, J = 7.4 Hz, H_3), 2.66 (3H, s, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.40 (d, J = 10.4 Hz), 154.04 (d, J = 7.1 Hz), 135.72 (d, J = 3.0 Hz), 134.22 (d, J = 10.5 Hz), 130.83, 130.67 (d, J = 13.2 Hz), 129.87, 128.65 (d, J = 85.9 Hz), 128.32, 128.11 (d, J = 8.8 Hz), 120.75 (q, J = 321.2 Hz), 120.37 (d, J = 4.5 Hz), 119.90, 115.82 (d, J = 90.3 Hz), 103.30, 83.97 (d, J = 6.1 Hz), 24.83; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.8; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 454.2, $C_{32}H_{25}NP^+$ requires 454.2.

(2-Fluoro-5-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2j)



Prepared according to general procedure A using 2-fluoro-5-methylpyridine (620 μL, 5.98 mmol), Tf_2O (1.00 mL, 5.95 mmol), PPh_3 (1.73 g, 6.55 mmol), DBU (890 μL, 5.95 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a white solid (2.54 g, 4.87 mmol, 82% yield). mp 160-161 ºC; IR ν_{max}/cm^{-1} (film): 3066, 1438, 1261, 1142, 1032, 720; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.43 (1H, d, J = 6.8 Hz, H_1), 7.96-7.88 (3H, m, H_5), 7.87-7.79 (6H, m, H_4), 7.75-7.67 (6H, m, H_3), 6.72 (1H, dd, 15.6, 2.8 Hz, H_2), 2.00 (3H, s, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.44 (dd, J = 244.1, 17.6 Hz), 152.46 (dd, J = 13.7, 10.7 Hz), 136.14 (d, J = 3.1 Hz), 134.41 (app t, J = 6.4 Hz), 134.11 (d, J = 10.7 Hz), 131.74 (dd, J = 83.1, 6.9 Hz), 131.20 (d, J = 13.0 Hz), 120.71 (q, J = 320.4 Hz), 115.43 (dd, J = 40.4, 11.4 Hz), 115.26 (d, J = 89.27 Hz), 18.97 (d, J = 3.8 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -66.58 (d, J = 9.4 Hz), -78.17; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.40 (d, J = 9.4 Hz); *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 372.2, $C_{24}H_{20}FNP^+$ requires 372.1.

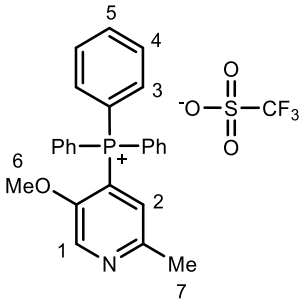
(5-Methoxy-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2k) and (3-methoxy-6-methylpyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (2k')



10:1 Mixture of Regioisomers

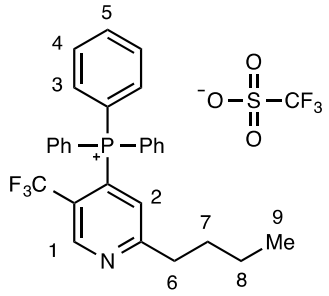
Prepared according to general procedure A using 5-methoxy-2-methylpyridine (397 mg, 3.23 mmol), Tf_2O (542 μL, 3.23 mmol), PPh_3 (931 mg, 3.35 mmol), DBU (482 μL, 3.23 mmol) and CH_2Cl_2 (32 mL). After the purification procedure, the title compounds (10:1 mixture of regioisomers) were isolated as a white solid (1.29 g, 2.43 mmol, 75% combined yield). An analytically pure sample of the major regioisomer was obtained by recrystallization from CH_2Cl_2 and Et_2O.

(5-Methoxy-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2k)



mp 211-212 ºC; IR ν_{max}/cm^{-1} (film): 3069, 2952, 1486, 1438, 1261, 1224, 1108, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (1H, d, *J* = 6.9 Hz, H_1), 7.95-7.40 (15H, m, H_3, H_4, and H_5), 6.79 (1H, d, *J* = 15.0 Hz, H_2), 3.62 (3H, s, H_6), 2.46 (3H, s, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.72, 153.05 (d, *J* = 10.7 Hz), 135.62 (d, *J* = 4.6 Hz), 135.46 (d, *J* = 3.1 Hz), 133.71 (d, *J* = 10.7 Hz), 130.51 (d, *J* = 13.0 Hz), 127.12 (d, *J* = 6.9 Hz), 120.72 (q, *J* = 321.21 Hz), 116.46 (d, *J* = 91.6 Hz), 115.62 (d, *J* = 87.0 Hz), 57.01, 23.55; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.13; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.36; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 384.2, $C_{25}H_{23}NOP^+$ requires 384.2.

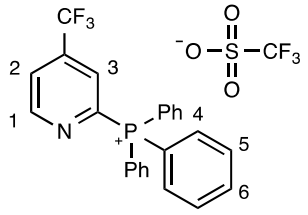
(2-Butyl-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2l)



Prepared according to general procedure A using 2-butyl-5-(trifluoromethyl)pyridine (1.02 g, 5.00 mmol), Tf_2O (845 μL, 5.00 mmol), PPh_3 (1.44 g, 5.50 mmol), DBU (758 μL, 5.00 mmol) and CH_2Cl_2 (50 mL). After the purification procedure, the title compound was isolated as a white solid (2.55 g, 4.16 mmol, 83% yield). mp 152-154 ºC; IR ν_{max}/cm^{-1} (film): 3057, 2931, 1717, 1437, 1414, 1260, 1222, 1147, 1105, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.16 (1H, d, *J* = 6.8 Hz, H_1), 7.92–7.87 (3H, m, H_5), 7.80–7.76 (6H, m, H_4), 7.73–7.67 (6H, m, H_3), 7.18 (1H, d, *J* = 17.2 Hz, H_2), 2.93 (2H, t, *J* = 7.6 Hz, H_6), 1.69–1.62 (2H, m, H_7), 1.37–1.27 (2H, m, H_8), 0.88 (3H, t, *J* = 7.2 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.99 (d, *J* = 9.7 Hz), 150.06 (m), 135.96 (d, *J* = 3.1

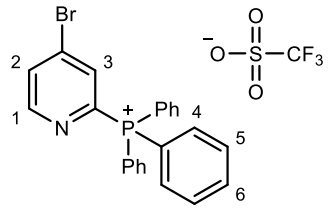
Hz), 134.41 (d, *J* = 10.4 Hz), 130.74 (d, *J* = 13.0 Hz), 129.77 (d, *J* = 8.5 Hz), 125.90 (d, *J* = 80.1, 1.0 Hz), 124.42 (qd, *J* = 33.1, 4.0 Hz), 122.49 (qd, *J* = 275.1, 2.9 Hz), 120.76 (q, *J* = 321.2 Hz), 116.40 (d, *J* = 90.4 Hz), 37.93, 30.35, 22.11, 13.63; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.27, -53.55; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 27.4 (d, *J* = 2.3 Hz); *m/z* LRMS found $[M]^+$ 305.2, $C_{28}H_{26}F_3NP^+$ requires 305.2.

Triphenyl(4-(trifluoromethyl)pyridin-2-yl)phosphonium trifluoromethanesulfonate (2m)



Prepared according to general procedure A using 4-(trifluoromethyl)pyridine (926 μL, 8.00 mmol), Tf_2O (1.35 mL, 8.00 mmol), PPh_3 (2.31 g, 8.80 mmol), DBU (1.20 mL, 8.00 mmol) and CH_2Cl_2 (80 mL). After the purification procedure, the title compound was isolated as an off-white solid (3.69 g, 6.62 mmol, 83% yield). mp 110–112 ºC; IR ν_{max}/cm^{-1} (film): 3071, 1588, 1485, 1390, 1223, 1180, 998, 572, 535; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.33 (1H, d, *J* = 2.8 Hz, H_1), 8.02 (1H, m, H_2), 7.92 (3H, m, H_6), 7.82–7.69 (13H, m, H_3, H_4, and H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.20 (d, *J* = 19.9 Hz), 147.00 (d, *J* = 121.0 Hz), 139.92 (qd, *J* = 35.8 Hz, 11.3 Hz), 136.02 (d, *J* = 2.9 Hz), 134.55 (d, *J* = 10.2 Hz), 130.70 (d, *J* = 13.1 Hz), 126.05 (dq, *J* = 25.9, 3.6 Hz), 124.36 (m), 121.47 (qd, *J* = 274.1, 3.0 Hz), 120.70 (q, *J* = 320.5 Hz), 115.93 (d, *J* = 90.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –64.7, –78.2 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.2; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 408.1, $C_{24}H_{18}F_3NP^+$ requires 408.1.

(4-bromopyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (2n)

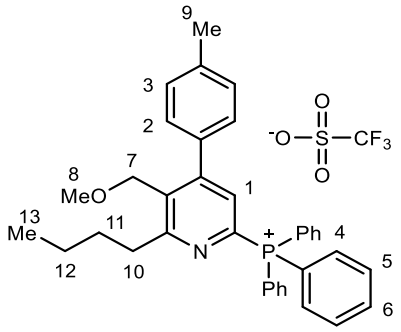


Prepared according to general procedure A[2] using 4-bromopyridine (198 μL, 2.00 mmol), Tf_2O (338 μL, 2.00 mmol), PPh_3 (577 mg, 2.20 mmol), DBU (303 μL, 2.00 mmol) and CH_2Cl_2 (40 mL). After the purification procedure,[3] the title compound was isolated as a tan solid (677 mg, 1.20 mmol, 60% yield). mp 147-149 ºC; IR ν_{max}/cm^{-1} (film): 3087, 3061, 1553, 1436, 1258, 1137, 1110, 1028, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.88 (1H, d, J = 5.1 Hz, H_1), 8.03-7.84 (4H, m, H_3 and H_6), 7.84-7.59 (13H, m, H_2, H_4, and H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.28 (d, J = 20.6 Hz), 146.37 (d, J = 119.1 Hz), 135.97 (d, J = 3.1 Hz), 135.16 (d, J = 14.4 Hz), 134.55 (d, J = 10.8 Hz), 134.00 (d, J = 25.2 Hz), 131.88 (d, J = 3.1 Hz), 130.69 (d, J = 13.6 Hz), 120.80 (q, J = 321.0 Hz), 116.21 (d, J = 89.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.1 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.6; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 418.1, $C_{23}H_{18}BrNP^+$ requires 418.0.

[2] A solution of 4-bromopyridine in CH_2Cl_2 (20 mL) was added to a solution of Tf_2O in CH_2Cl_2 (20 mL) at –78 ºC over 10 minutes instead of the order of addition in General Procedure A.

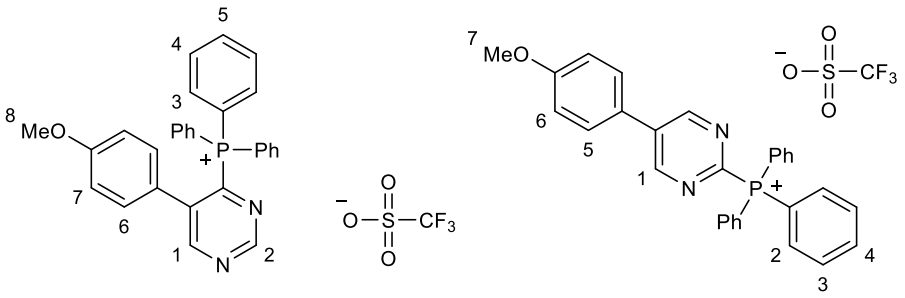
[3] Once the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*, the title compound was isolated by recrystallization from CH_2Cl_2 and Et_2O, instead of precipitated according to General Procedure A.

(6-Butyl-5-(methoxymethyl)-4-(*p*-tolyl)pyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (2o)



Prepared according to general procedure A using 2-butyl-3-(methoxymethyl)-4-(*p*-tolyl)pyridine (483 mg, 1.79 mmol), Tf_2O (300 μL, 1.79 mmol), PPh_3 (517 mg, 1.97 mmol), DBU (268 μL, 1.79 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a white solid (909 mg, 1.34 mmol, 75% yield). mp 149-150 ºC; IR ν_{max}/cm^{-1} (film): 3059, 2956, 2869, 1568, 1438, 1261, 1151, 1031 ; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.91-7.82 (3H, m, H_6), 7.78-7.62 (12H, m, H_5 and H_4), 7.35 (1H, d, J = 6.4 Hz, H_1), 7.26-7.23 (4H, m, H_3 and H_2), 4.35 (2H, s, H_7), 3.38 (3H, s, H_8), 3.06 (2H, t, J = 7.7 Hz, H_{10}), 2.35 (3H, s, H_9), 1.71 (2H, qn, J = 7.7 Hz, H_{11}), 1.33 (2H, sext, J = 7.6 Hz, H_{12}), 0.87 (3H, t, J = 7.5 Hz, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.00 (d, J = 19.1 Hz), 152.58 (d, J = 11.4 Hz), 143.18, 141.99, 139.39, 135.63 (d, J = 3.1 Hz), 134.47 (d, J = 10.7 Hz), 133.60 (d, J = 1.5 Hz), 133.19 (d, J = 3.8 Hz), 130.42 (d, J = 13.0 Hz), 129.91 (d, J = 25.2 Hz), 129.04 (d, J = 84.7 Hz), 120.83 (q, J = 321.2 Hz), 117.07 (d, J = 89.27 Hz), 67.93, 58.68, 34.27, 30.58, 22.31, 21.08, 13.83; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.07; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 14.49; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 530.3, $C_{36}H_{37}NOP^+$ requires 530.3.

(5-(4-Methoxyphenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2p) and (5-(4-methoxyphenyl)pyrimidin-2-yl)triphenylphosphonium trifluoromethanesulfonate (2p')



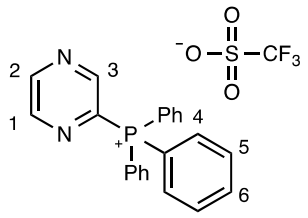
24:1 Mixture of Regioisomers

Prepared according to general procedure A (except that the stirring time after addition of PPh_3 was 1 hour instead of 30 minutes) using 5-(4-methoxyphenyl)pyrimidine (450 mg, 2.42 mmol), Tf_2O (409 μL, 2.42 mmol), PPh_3 (698 mg, 2.66 mmol), DBU (367 μL, 2.42 mmol) and CH_2Cl_2 (24 mL). After the purification procedure,[4] the title compound was isolated as a tan solid (724 mg, 1.21 mmol, 50% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3063, 2936, 1396, 1258, 1222, 1146, 1105, 1028, 634; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.44 (1H, s, H_2), 8.98 (1H, d, J = 9.0 Hz, H_1), 7.80-7.70 (3H, m, H_5), 7.67-7.56 (12H, m, H_3 and H_4), 6.91 (2H, d, J = 8.7 Hz, H_6), 6.55 (2H, d, J = 8.7 Hz, H_7), 3.72 (3H, s, H_8); Minor isomer, ^1H NMR (400

[4] The concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of chilled Et_2O (0 °C) instead of the order of addition in General Procedure A. The mixture was then placed in a -20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled Et_2O (0 °C). The solid was redissolved in approximately 10 mL of CH_2Cl_2 and was precipitated a second time via dropwise addition to an excess of chilled Et_2O (0 °C). The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt.

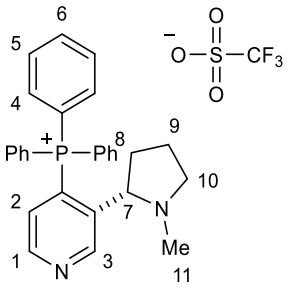
MHz, $CDCl_3$) δ: 9.23 (2H, s, H_1), 7.80-7.70 (3H, m, H_4), 7.70 (2H, d, J = 8.7 Hz, H_5), 7.67-7.56 (12H, m, H_2 and H_3), 7.09 (2H, d, J = 8.6 Hz, H_6), 3.88 (3H, s, H_7); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.84 (d, J = 5.3 Hz), 160.53, 156.97 (d, J = 16.8 Hz), 149.74 (d, J = 114.5 Hz), 142.72 (d, J = 19.2 Hz), 135.22 (d, J = 3.1 Hz), 134.67 (d, J = 10.2 Hz), 130.60, 130.25 (d, J = 13.1 Hz), 123.61, 120.82 (q, J = 321.3 Hz), 117.10 (d, J = 88.6 Hz), 114.37, 55.42; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.01; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.84; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 447.2, $C_{29}H_{24}N_2OP^+$ requires 447.2.

Triphenyl(pyrazin-2-yl)phosphonium trifluoromethanesulfonate (2q)



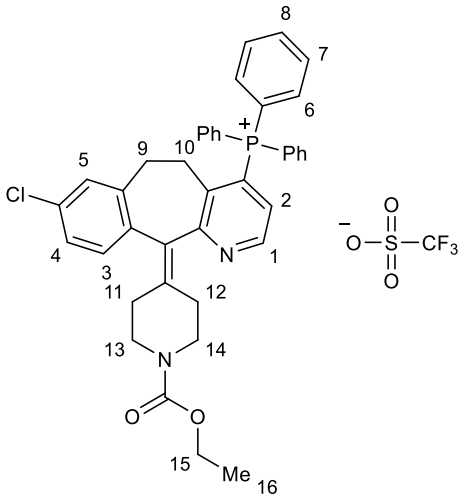
Prepared according to general procedure A using pyrazine (120 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), PPh_3 (432 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol) and CH_2Cl_2 (13.0 mL). After the purification procedure, the title compound was isolated as an off-white solid (525 mg, 1.07 mmol, 80% yield). mp 185–188 ºC; IR ν_{max}/cm^{-1} (film): 3066, 1587, 1484, 1395, 1186, 617, 571; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.09 (1H, br s), 9.06 (1H, br s), 8.86 (1H, br s), 7.91 (3H, m), 7.82–7.71 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.72 (d, J = 24.0 Hz), 149.51 (d, J = 3.4 Hz), 147.25 (d, J = 14.7 Hz), 141.37 (d, J = 115.4 Hz), 136.02 (d, J = 3.1 Hz), 134.54 (d, J = 10.4 Hz), 130.71 (d, J = 13.1 Hz), 120.69 (q, J = 321.1 Hz), 115.71 (d, J = 89.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 13.9; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 341.1, $C_{22}H_{18}N_2P^+$ requires 341.1.

(*S*)-(3-(1-methylpyrrolidin-2-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (4)



Prepared according to general procedure A using (-)-nicotine (803 μL, 5.00 mmol), Tf_2O (845 μL, 5.00 mmol), PPh_3 (1.44 g, 5.50 mmol), DBU (748 μL, 5.00 mmol) and CH_2Cl_2 (50 mL). After the purification procedure, the title compound was isolated as a tan solid (2.19 g, 3.82 mmol, 76% yield). mp 178-181 ºC; IR ν_{max}/cm^{-1} (film): 3066, 2971, 2758, 1338, 1264, 1223, 1142, 1108, 1102, 1031, 719, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.37 (1H, d, J = 6.9 Hz, H_3), 8.79 (1H, app t, J = 4.6 Hz, H_1), 7.96-7.62 (15H, m, H_4, H_5, and H_6), 7.12 (1H, dd, J = 15.5, 5.1 Hz, H_2), 3.10-2.93 (2H, m, H_7 and H_{10}), 1.99 (1H, app q, J = 8.5 Hz, H_{10}), 1.87-1.67 (4H, m, H_9 and H_{11}), 1.49-1.23 (2H, m, H_8 and H_9), 1.01-0.83 (1H, m, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.01 (d, J = 8.1 Hz), 149.96 (d, J = 10.6 Hz), 144.24 (d, J = 6.7 Hz), 135.99 (d, J = 3.0 Hz), 134.39 (d, J = 10.2 Hz), 131.05 (d, J = 13.0 Hz), 127.53 (d, J = 9.9 Hz), 126.24 (d, J = 81.6 Hz), 120.83 (q, J = 321.3 Hz), 116.74 (d, J = 88.5 Hz), 66.03 (d, J = 4.9 Hz), 55.97, 39.39, 35.43, 22.93; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -77.01; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.69; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 423.2, $C_{28}H_{28}N_2P^+$ requires 423.2.

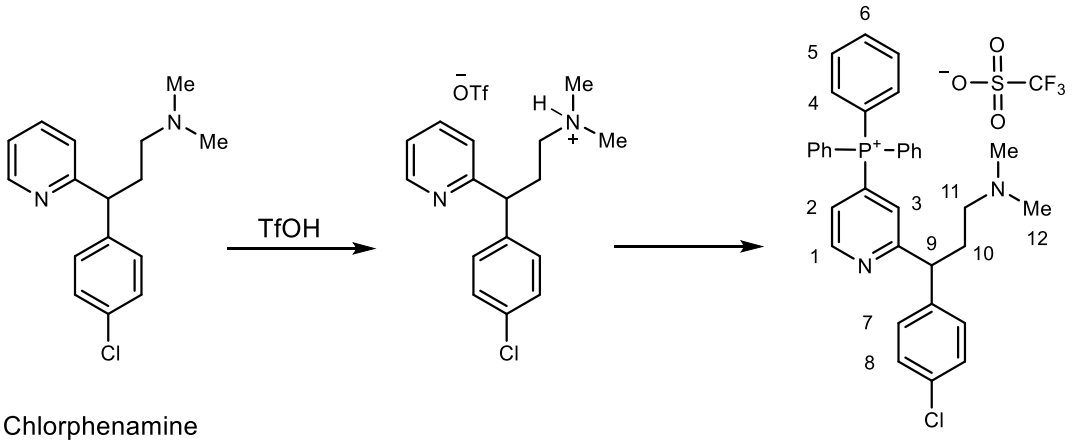
(8-Chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (6)



Prepared according to general procedure A using Loratadine (ethyl-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-b]pyridine-11-ylidene)-1-piperidinecarboxylate) (750 mg, 1.96 mmol), Tf_2O (329 μL, 1.96 mmol), PPh_3 (565 mg, 2.15 mmol), DBU (300 μL, 1.96 mmol) and CH_2Cl_2 (20 mL). After the purification procedure, the title compound was isolated as a white solid (1.37 g, 1.72 mmol, 88% yield). mp 129-136 ºC; IR ν_{max}/cm^{-1} (film): 3061, 2978, 2908, 2868, 1437, 1261, 1221, 1147, 1106, 1029, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, app t, J = 5.0 Hz, H_1), 7.97-7.87 (3H, m, H_8), 7.86-7.74 (6H, m, H_7), 7.73-7.60 (6H, m, H_6), 7.16-7.01 (3H, m, H_2, H_3, and H_4), 6.71 (1H, s, H_5), 4.14 (2H, q, J = 7.0 Hz, H_{15}), 3.84-3.61 (2H, m, H_{13} or H_{14}), 3.45-3.20 (3H, m, H_{10} and H_{13} or H_{14}), 2.75 (1H, dt, J = 17.4, 4.7 Hz, H_9), 2.58 (1H, dt, J = 14.9, 4.7 Hz, H_{10}), 2.53-2.30 (3H, m, H_{11} or H_{12}), 2.26-2.09 (1H, m, H_{11} or H_{12}), 1.60-1.43 (1H, m, H_9), 1.25 (3H, t, J = 7.2 Hz, H_{16}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.64 (d, J = 8.3 Hz), 155.37, 149.08 (d, J = 11.4 Hz), 139.23, 136.84, 136.66 (d, J = 6.8 Hz), 136.06 (d, J = 3.1 Hz),

134.21 (d, J = 10.7 Hz), 133.95, 133.57, 132.37, 131.58, 131.13 (d, J = 13.0 Hz), 129.85, 127.22 (d, J = 10.0 Hz), 127.01 (d, J = 82.2 Hz), 126.43, 120.78 (q, J = 321.3 Hz), 116.42 (d, J = 88.5 Hz), 61.39, 44.65, 44.41, 30.74, 30.46, 30.39, 29.39, 14.59; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.16; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.17; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 643.2, $C_{40}H_{37}ClN_2O_2P^+$ requires 643.2.

(2-(1-(4-Chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (8)

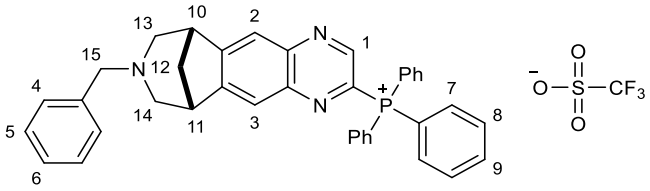


Chlorphenamine

Chlorphenamine (1.64 g, 5.95 mmol) was dissolved in Et_2O (10 mL) and cooled to 0 ºC. Trifluoromethanesulfonic acid (527 µL, 5.95 mmol) was added dropwise, the ice bath was removed, and the solution was stirred for 10 minutes at room temperature. The solution was concentrated *in vacuo* and the resulting acid salt was subjected to general procedure A (expect that the product was precipitated a second time using the same protocol and the product suspension was placed in a -20 °C refrigerator for 12 hours instead of 1) using Tf_2O (1.0 mL, 5.95 mmol), PPh_3 (1.73 g, 6.55 mmol), DBU (1.78 mL, 11.90 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a yellow solid (1.63 g, 2.38 mmol, 40% yield). mp

52-58 ºC; IR ν_{max}/cm^{-1} (film): 3062, 2941, 2818, 2770, 1438, 1260, 1108, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.97 (1H, app t, J = 5.1 Hz, H_1), 7.93-7.86 (3H, m, H_6), 7.80-7.70 (6H, m, H_5), 7.61-7.50 (6H, m, H_4), 7.39 (1H, ddd, J = 12.8, 5.1, 1.5 Hz, H_2), 7.25-7.16 (5H, m, H_3, H_7, and H_8), 4.28 (1H, app t, J = 6.8 Hz, H_9), 2.56-2.43 (1H, m, H_{10}), 2.32-2.11 (9H, m, H_{10}, H_{11}, and H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.55 (d, J = 9.9 Hz), 150.97 (d, J = 9.9 Hz), 140.26, 135.82 (d, J = 3.1 Hz), 134.02 (d, J = 10.7 Hz), 132.25, 130.61 (d, J = 13.0 Hz), 128.92 (d, J = 85.5 Hz), 128.75, 127.92, 126.26 (d, J = 8.4 Hz), 124.42 (d, J = 7.6 Hz), 120.46 (q, J = 321.2 Hz), 115.31 (d, J = 89.3 Hz), 56.73, 49.77, 44.88, 31.99; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.14; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.38; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 535.2, $C_{34}H_{33}ClN_2P+$ requires 535.2.

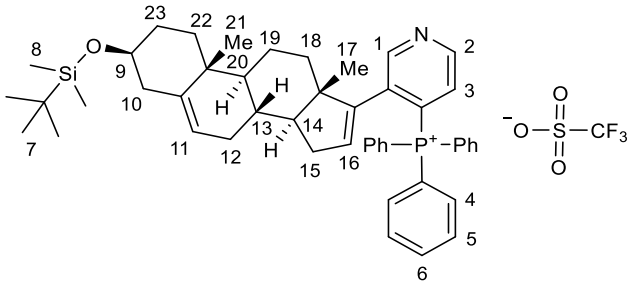
((*rac*)-8-benzyl-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-g]quinoxalin-2-yl)triphenylphosphonium trifluoromethanesulfonate (10)



Prepared according to general procedure A (except that after the addition of PPh_3 the reaction mixture was heated to 40 °C for 1 hour, followed by addition of DBU at 40 °C instead of –78 °C) using 8-benzyl-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-g]quinoxaline (115 mg, 0.38 mmol), Tf_2O (64 μL, 0.38 mmol), PPh_3 (110 mg, 0.42 mmol), DBU (57 μL, 0.38 mmol) and CH_2Cl_2 (3.8 mL). After the purification procedure,[5] the title compound was isolated as a tan solid

(158 mg, 0.22 mmol, 58% yield). mp 101-106 ºC; IR ν_{max}/cm^{-1} (film): 3061, 2949, 2900,2797, 1439, 1262, 1148, 1109, 1029, 636; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.09 (1H, s, H_1), 8.10-7.72 (17H, m, H_2, H_3, H_7, H_8, and H_9), 7.20-7.05 (3H, m, H_5 and H_6), 6.92-6.80 (2H, m, H_4), 3.55-3.27 (4H, m, H_{15}, H_{10}, and H_{11}), 3.03-2.87 (2H, m, H_{13} or H_{14}), 2.66-2.42 (2H, m, H_{13} or H_{14}), 2.29-2.15 (1H, m, H_{12}), 1.87 (1H, d, *J* = 10.8 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$)[6] δ: 144.90 (d, *J* = 23.5 Hz), 144.21, 143.45 (d, *J* = 16.9 Hz), 137.51 (br s), 136.00 (d, *J* = 2.9 Hz), 134.55 (d, *J* = 10.9 Hz), 130.72 (d, *J* = 13.0 Hz), 129.20-126.21 (3C, m), 120.69 (br s), 120.67 (q, *J* = 321.5 Hz), 116.42 (d, *J* = 88.3 Hz), 61.29, 57.90-56.06 (2C, m), 43.14-40.43 (3C, m); ^{19}F NMR (365 MHz, DMSO-d_6) δ: –77.80; ^{31}P NMR (162 MHz, DMSO-d_6) δ: 13.81; *m/z* LRMS found $[M+H]^+$ 562.2, $C_{38}H_{33}N_3P^+$ requires 562.2.

(3-((8*R*,9*S*,10*R*,13*S*,14*S*)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (12)

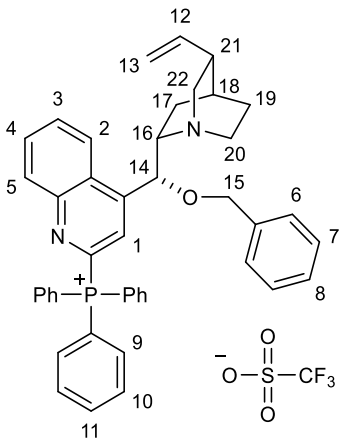


[5] The concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of chilled Et_2O (0 °C) instead of the order of addition in General Procedure A. The mixture was then placed in a -20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled Et_2O (0 °C). The solid was redissolved in approximately 10 mL of CH_2Cl_2 and was precipitated a second time via dropwise addition to an excess of chilled Et_2O (0 °C). The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt.

[6] Please note that the ^{13}C NMR contains a number of broad peaks that account for the lower than expected number of carbon resonances. ^{13}C NMR does not improve with an increase in number of scans or by varying concentration.

Prepared according to general procedure A (except that the reaction was warmed to -50 ºC before the addition of PPh_3, was stirred at -50 °C for 1 hour, and DBU was added at -50 °C instead of -78 °C. During the purification stage the product suspension was placed in a -20 ºC refrigerator for approximately 12 hours instead of 1) using 3-((8*R*,9S,10*R*,13S,14*S*)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)pyridine (295 mg, 0.64 mmol), Tf_2O (107 μL, 0.64 mmol), PPh_3 (184 mg, 0.70 mmol), DBU (95 μL, 0.64 mmol) and CH_2Cl_2 (6.5 mL). After the purification procedure, the title compound was isolated as a white solid (412 mg, 0.47 mmol, 74% yield). mp 158-163 ºC; IR ν_{max}/cm^{-1} (film): 3062, 2929, 1442, 1259, 1096, 1030, 909, 725; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.02 (1H, d, J = 7.2 Hz), 8.75 (1H, t, J = 4.6 Hz), 7.92-7.83 (3H, m), 7.83-7.73 (6H, m), 7.72-7.61 (6H, m), 7.33-7.24 (1H, m), 5.57 (1H, br s), 5.24 (1H, d, J = 4.4 Hz), 3.49 (1H, m), 2.30-2.10 (2H, m), 1.89-1.66 (6H, m), 1.62-0.71 (22H, m), 0.65-0.51 (1H, dt, J = 11.7 Hz, 4.92 Hz), 0.06 (6H, s), -0.12-(-0.23) (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.77 (d, J = 7.6 Hz), 149.14 (d, J = 3.8 Hz), 148.73 (d, J = 10.7 Hz), 141.78, 139.29, 137.51 (d, J = 6.1 Hz), 135.66 (d, J = 3.1 Hz) 134.31 (d, J = 9.9 Hz), 130.93 (d, J = 13.0 Hz), 129.99 (d, J = 10.7 Hz), 125.29 (d, J = 83.9 Hz), 120.84 (q, J = 328.8 Hz), 120.18, 118.03 (d, J = 90.0 Hz), 72.31, 55.45, 49.91, 48.91, 42.68, 37.24, 36.58, 33.70, 32.64, 31.92, 31.17, 29.97, 25.92, 20.42, 19.20, 18.79, 18.24, -4.58; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.11; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.78; *m/z* LRMS found $[M+H]^+$ 724.4, $C_{48}H_{59}NOPSi^+$ requires 724.4.

(4-((*R*)-(Benzyloxy)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (14)

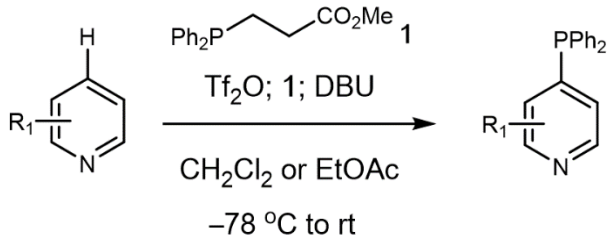


Prepared according to general procedure A (except that the stirring time after addition of PPh_3 was 1 hour instead of 30 minutes) using (1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(benzyloxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (472 mg, 1.23 mmol), Tf_2O (207 μL, 1.23 mmol), PPh_3 (354 mg, 1.35 mmol), NEt_3 (171 μL, 1.23 mmol) and CH_2Cl_2 (12 mL). After the purification procedure,[7] the title compound was isolated as a yellow solid (507 mg, 0.638 mmol, 52% yield). mp 92-98 ºC; IR ν_{max}/cm^{-1} (film): 3062, 3031, 2940, 2866, 1144, 1108, 1029, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, J = 8.1 Hz, H_5), 8.26 (1H, d, J = 8.6 Hz, H_2), 7.94 (1H, t, J = 7.2 Hz, H_3), 7.91-7.60 (17H, m, H_1, H_4, H_9, H_{10}, and H_{11}), 7.29-7.02 (3H, m, H_7 and H_8), 7.14-7.02 (2H, m, H_6), 5.83-5.45 (2H, m, H_{12} and H_{14}), 5.07-4.89 (2H, m, H_{13}), 4.60 (1H, d, J = 11.4 Hz, H_{15}), 4.33 (1H, d, J = 11.4 Hz, H_{15}), 3.52-3.06 (3H, m, H_{16}, H_{20}, and H_{22}), 2.84-2.62 (2H, m, H_{20} and H_{22}), 2.49-2.33

[7] The concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of chilled hexanes (0 °C) instead of the order of addition in General Procedure A. The mixture was then placed in a -20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled hexanes (0 °C). The solid was redissolved in approximately 10 mL of CH_2Cl_2 and was precipitated a second time via dropwise addition to an excess of chilled hexanes (0 °C). The resulting suspension was filtered on a frit, the solid washed with chilled hexanes (0 °C) and dried *in vacuo* to provide the pure phosphonium salt.

(1H, br s, H_{21}), 2.06-1.47 (5H, m, H_{17}, H_{18}, H_{19}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.20 (d, *J* = 22.1 Hz), 148.45, 145.10, 143.93, 139.54, 136.58, 135.68 (d, *J* = 3.0 Hz), 134.53 (d, *J* = 10.0 Hz), 131.99-131.79 (3C, m), 131.23, 130.44 (d, *J* = 13.2 Hz), 128.40, 127.89, 127.22, 126.71 (d, *J* = 3.1 Hz), 126.08, 123.78, 120.64 (q, *J* = 320.3 Hz), 116.99 (d, *J* = 87.7 Hz), 115.55, 71.81, 60.71, 55.61, 43.04, 38.32, 26.89, 25.83; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 14.92; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 645.3, $C_{44}H_{42}N_2OP^+$ requires 645.3.

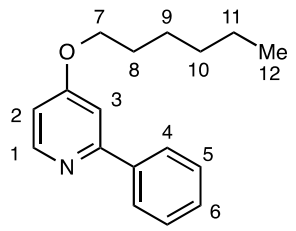
A 1.3.2 General Procedure B (Preparation of Heteroaryl Ethers)



An oven dried 8 mL vial with a septa cap was charged with sodium hydride (60% dispersion in mineral oil, 1.5 equiv) and placed under a nitrogen atmosphere. THF (0.5 M) was added, the suspension was cooled to 0 ºC and the alcohol (1.5 equiv) was added dropwise over 5 minutes (if the alcohol was a solid or viscous liquid, it was added as a 1.0 M solution in THF to an equivalent volume 1.0 M solution of NaH in THF). The reaction was stirred for 30 minutes before the septa cap was briefly removed and the phosphonium salt (1.0 equiv) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill, the ice bath removed, and the reaction stirred for 12 hours while warming to room temperature. The reaction was quenched with H_2O, the aqueous layer was separated and extracted with Et_2O (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$),

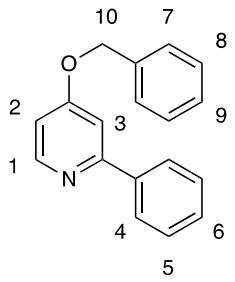
filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl ether product.

4-(Hexyloxy)-2-phenylpyridine (3da)



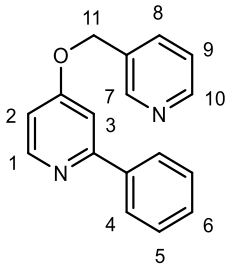
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white amorphous solid (92 mg, 0.36 mmol, 72% yield). mp 36-37 ºC; IR ν_{max}/cm^{-1} (film):3068, 2942, 1563, 1467, 1323, 1219, 1021; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, d, J = 5.5 Hz, H_1), 7.97 (2H, d, J = 7.4 Hz, H_4), 7.46 (2H, t, J = 7.4 Hz, H_5), 7.40 (1H, t, J = 7.4 Hz, H_6), 7.22 (1H, d, J = 2.4 Hz, H_3), 6.74 (1H, dd, J = 5.7, 2.2 Hz, H_2), 4.05 (2H, t, J = 6.5 Hz, H_7) 1.82 (2H, qn, J = 6.5 Hz, H_8), 1.48 (2H, qn, J = 6.7 Hz, H_9), 1.40-1.31 (4H, m, H_{10} and H_{11}), 0.92 (3H, t, J = 7.0 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.83, 159.08, 150.79, 139.49 128.84, 128.57, 126.87, 108.45, 107.25, 67.92, 31.45, 28.86, 25.57, 22.52, 13.95; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 256.2, $C_{17}H_{22}NO^+$ requires 256.2.

4-(benzyloxy)-2-phenylpyridine 2-phenylpyridin-4-ol (3db)



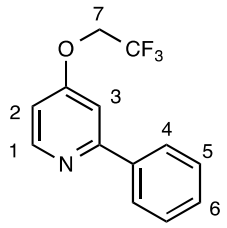
Prepared according to general procedure B (except that CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), benzyl alcohol (78 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (282 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 5% to 15% EtOAc in hexanes) to afford the title compound as a faintly purple amorphous solid (94 mg, 0.36 mmol, 72% yield). mp 71–73 ºC; IR ν_{max}/cm^{-1} (film): 3030, 2937, 2871, 1961, 1495, 1421, 1250, 1121, 1079, 1029, 646, 548; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.53 (1H, d, J = 5.7 Hz, H_1), 7.95 (2H, d, J = 7.6 Hz, H_4), 7.50–7.35 (8H, m, H_5, H_6, H_7, H_8, H_9), 7.32 (1H, d, J = 1.7 Hz, H_3), 6.85 (1H, dd, J = 5.4, 2.2 Hz, H_2), 5.18 (2H, s, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.44, 159.16, 150.87, 139. .29, 135.66, 128.93, 128.67, 128.59, 128.30, 1 27.46, 126.86, 108.70, 107.57, 69.78. The spectroscopic data is in agreement with a reported synthesis.[3] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 262.1, $C_{18}H_{16}NO^+$ requires 262.1.

2-Phenyl-4-(pyridin-3-ylmethoxy)pyridine (3dc)



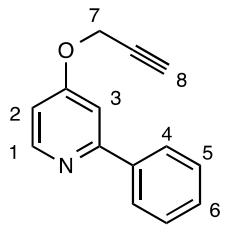
Prepared according to general procedure B (except that CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), pyridin-3-ylmethanol (73 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283mg, 0.50 mmol) and THF (1.0 mL). Prior to flash chromatography the crude reaction product was dissolved in methanol (5.0 mL) and a methanolic solution of hydrochloric acid (5.0 mL of 4.2 M solution) was added dropwise. The resulting mixture was concentrated *in vacuo* and dry loaded onto a silica gel column (elution: 2.5% MeOH in CH_2Cl_2, then 30 mL of NEt_3, then EtOAc) afforded the title compound as a pink amorphous solid (84 mg, 0.32 mmol, 64% yield). mp 90-91 ºC; IR ν_{max}/cm^{-1} (film): 3027, 2984, 1561, 1207, 1013, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (1H, s, H_7), 8.61 (1H, d, J = 4.6 Hz, H_{10}), 8.52 (1H, d, J = 5.7 Hz, H_1), 7.94 (2H, d, J = 7.5 Hz, H_4), 7.76 (1H, d, J = 7.7 Hz, H_8), 7.48-7.36 (3H, m, H_5 and H_6), 7.33 (1H, dd, J = 7.7, 4.7 Hz, H_9), 7.29 (1H, d, J = 2.3 Hz, H_3), 6.81 (1H, dd, J = 5.7, 2.3 Hz, H_2), 5.15 (2H, s, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.07, 159.28, 150.95, 149.78, 148.93, 139.07, 135.23, 131.26, 129.05, 128.62, 126.84, 123.53, 108.52, 107.36, 67.27; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 263.2, $C_{17}H_{15}N_2O^+$ requires 263.1.

2-Phenyl-4-(2,2,2-trifluoroethoxy)pyridine (3dd)



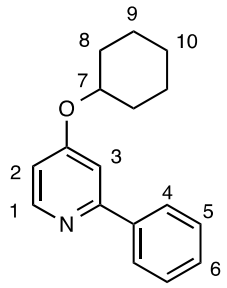
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 2,2,2-trifluoroethan-1-ol (57 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 15% EtOAc in hexanes) afforded the title compound as an off white amorphous solid (100 mg, 0.40 mmol, 79% yield). mp 50-51 ºC; IR ν_{max}/cm^{-1} (film): 3095, 2975, 1568, 1271, 1164, 978, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (1H, d, J = 5.6 Hz, H_1), 7.96 (2H, d, J = 7.4 Hz, H_4), 7.49-7.40 (3H, m, H_5 and H_6), 7.26 (1H, d, J = 2.4 Hz, H_3), 6.77 (1H, dd, J = 5.6, 2.4 Hz, H_2), 4.43 (2H, q, J = 7.9 Hz, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.99, 159.68, 151.21, 138.79, 129.31, 128.71, 126.90, 122.9 (q, J = 227.7 Hz), 108.07, 107.15, 64.9 (q, J = 35.9 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -73.70. The spectroscopic data is in agreement with a reported synthesis.[4] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 254.1, $C_{13}H_{11}F_3NO^+$ requires 254.1.

2-Phenyl-4-(prop-2-yn-1-yloxy)pyridine (3de)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), prop-2-yn-1-ol (43 μL, 0.75 mmol), triphenyl-(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the title compound as a yellow oil (68 mg, 0.33 mmol, 65% yield). IR ν_{max}/cm^{-1} (film): 3296, 3055, 2923, 1589, 1474, 1196, 1019; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, J = 5.6 Hz, H_1), 7.96 (2H, d, J = 7.4 Hz, H_4), 7.50-7.38 (3H, m, H_5 and H_6), 7.31 (1H, d, J = 2.4 Hz, H_3), 6.84 (1H, dd, J = 5.6, 2.4 Hz, H_2), 4.78 (2H, d, J = 2.3 Hz, H_7), 2.60 (1H, t, J = 2.3 Hz, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.29, 159.27, 150.88, 139.21, 129.03, 128.65, 126.91, 108.69, 107.45, 77.27, 76.62, 55.49. The spectroscopic data is in agreement with a reported synthesis.[5] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 210.1, $C_{14}H_{12}NO^+$ requires 210.1.

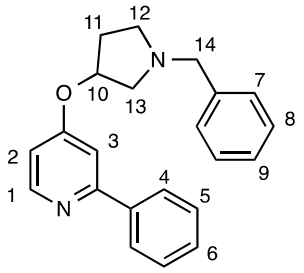
4-(Cyclohexyloxy)-2-phenylpyridine (3df)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), cyclohexanol (78 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (282 mg, 0.50 mmol) and THF (1.0 mL). The reaction was stirred for 13 hours after the addition of the phosphonium salt. Flash column chromatography (basic alumina: 6% EtOAc in hexanes) afforded the title compound as an amorphous white solid

(107 mg, 0.42 mmol, 85% yield). mp 49-50 ºC; IR ν_{max}/cm^{-1} (film): 3032, 2939, 1559, 1476, 1211, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (1H, d, J = 5.7 Hz, H_1), 7.95 (2H, d, J = 7.5 Hz, H_4), 7.49-7.37 (3H, m, H_5 and H_6), 7.21 (1H, d, J = 2.2 Hz, H_3), 6.74 (1H, dd, J = 5.7, 2.2 Hz, H_2), 4.42 (1H, m, H_7), 2.07-1.96 (2H, m, H_8), 1.89-1.77 (2H, m, H_9), 1.67-1.53 (3H, m, H_8 and H_{10}), 1.48-1.30 (3H, m, H_9 and H_{10}) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.70, 159.17, 150.80, 139.56, 128.80, 128.56, 126.88, 109.18, 108.30, 75.16, 31.40, 25.38, 23.51; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 254.2, $C_{17}H_{20}NO^+$ requires 254.2.

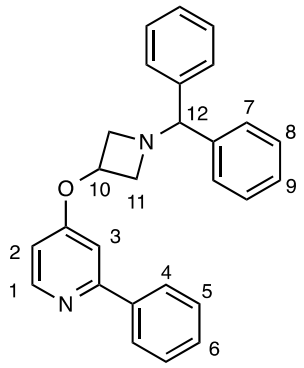
4-((1-Benzylpyrrolidin-3-yl)oxy)-2-phenylpyridine (3dg)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 1-benzylpyrrolidin-3-ol (124 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (basic alumina, gradient elution: 10% EtOAc in hexanes to 30% EtOAc in hexanes) afforded the title compound as a yellow oil (125 mg, 0.38 mmol, 75% yield). IR ν_{max}/cm^{-1} (film): 3029, 2920, 2792, 1559,1207, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (1H, d, J = 5.7 Hz, H_1), 7.96 (2H, d, J = 7.5 Hz, H_4), 7.52-7.23 (8H, m, H_5, H_6, H_7, H_8, and H_9), 7.19 (1H, d, J = 2.1 Hz, H_3), 6.68 (1H, dd, J = 5.7, 2.1 Hz, H_2), 4.98-4.86 (1H, m, H_{10}), 3.72 (1H, d, J = 12.7 Hz, H_{14}), 3.66 (1H, d, J = 12.7 Hz, H_{14}), 2.99 (1H, dd, J = 10.6, 6.1 Hz, H_{13}), 2.88-2.73

(2H, m, H_{12} and H_{13}), 2.59 (1H, app q, J = 7.6 Hz, H_{12}), 2.42-2.29 (1H, m, H_{11}), 2.09-1.96 (1H, m, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.53, 159.07, 150.78, 139.34, 138.31, 128.87, 128.71, 128.56, 128.23, 127.04, 126.82, 108.99, 108.02, 76.78, 60.06, 59.77, 52.56, 32.05; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 331.2, $C_{22}H_{23}N_2O^+$ requires 331.2.

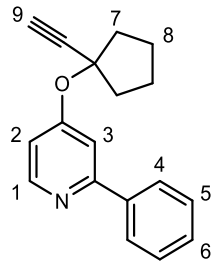
4-((1-Benzhydrylazetidin-3-yl)oxy)-2-phenylpyridine (3dh)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 1-benzhydrylazetidin-3-ol (180 mg, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 30% EtOAc in hexanes) afforded the title compound as a yellow oil (158 mg, 0.40 mmol, 80% yield). IR ν_{max}/cm^{-1} (film): 3027, 2954, 2838, 1592, 1211, 906, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (1H, d, J = 5.5 Hz, H_1), 7.92 (2H, d, J = 7.4 Hz, H_4), 7.48-7.38 (7H, m, H_5, H_6, and H_7), 7.30 (4H, app t, J = 7.4 Hz, H_8), 7.21 (2H, t, J = 7.4 Hz, H_9), 7.10 (1H, d, J = 2.3 Hz, H_3), 6.61 (1H, dd, J = 5.5, 2.3 Hz, H_2), 4.93 (1H, app qn, J = 5.6 Hz, H_{10}), 4.45 (1H, s, H_{12}), 3.76 (2H, app t, J = 5.6 Hz, H_{11}), 3.18 (2H, app t, J = 5.6 Hz, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.96, 159.39, 150.98,

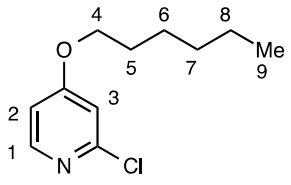
141.67, 139.26, 129.05, 128.68, 128.55, 127.39, 127.34, 126.90, 108.68, 107.31, 78.28, 66.32, 60.16; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 393.2, $C_{27}H_{25}N_2O^+$ requires 393.2.

4-((1-Ethynylcyclopentyl)oxy)-2-phenylpyridine (3di)



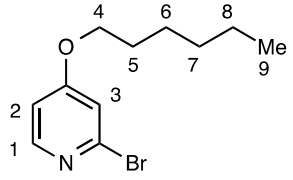
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 1-ethynylcyclopentan-1-ol (85 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a yellow oil (93 mg, 0.35 mmol, 71% yield). IR ν_{max}/cm^{-1} (film): 3292, 3032, 2960, 1590, 1472, 1189, 992; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, d, J = 5.6 Hz, H_1), 7.96 (2H, d, J = 7.8 Hz, H_4), 7.55-7.35 (4H, m, H_3, H_5 and H_6), 7.05 (1H, dd, J = 5.6, 2.4 Hz, H_2), 2.73 (1H, s, H_9), 2.43-2.33 (2H, m, H_7), 2.25-2.15 (2H, m, H_7), 1.86-1.78 (4H, m, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.79, 158.76, 150.34, 139.51, 128.80,128.58, 126.85, 111.58, 110.10, 84.05, 80.99, 75.58, 40.73, 23.79; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 264.2, $C_{18}H_{18}NO^+$ requires 264.1.

2-Chloro-4-(hexyloxy)pyridine (3aa)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-chloropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (262 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 4% EtOAc in hexanes to 8% EtOAc in hexanes) afforded the title compound as a yellow oil (82 mg, 0.34 mmol, 77% yield). IR ν_{max}/cm^{-1} (film): 2930, 1584, 1460, 1304, 1070, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (1H, d, J = 5.7 Hz, H_1), 6.80 (1H, d, J = 2.2 Hz, H_3), 6.71 (1H, dd, J = 5.7, 2.2 Hz, H_2), 3.98 (2H, t, J = 6.7 Hz, H_4), 1.77 (2H, qn, J = 6.9 Hz, H_5), 1.43 (2H, qn, J = 6.9 Hz, H_6), 1.37-1.27 (4H, m, H_7 and H_8), 0.89 (3H, t, J = 6.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.76, 152.52, 150.13, 110.03, 109.78, 68.53, 31.37, 28.66, 25.46, 22.48, 13.92. The spectroscopic data is in agreement with a reported synthesis.[6] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 214.1, $C_{11}H_{17}ClNO^+$ requires 214.1.

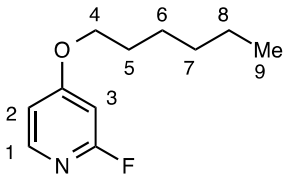
2-Bromo-4-(hexyloxy)pyridine (3ba)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-bromopyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (284 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 2.5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a pale orange oil (103 mg, 0.40 mmol, 80% yield). IR ν_{max}/cm^{-1} (film): 2929, 1580, 1302, 1062, 834; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (1H, d, J = 5.7

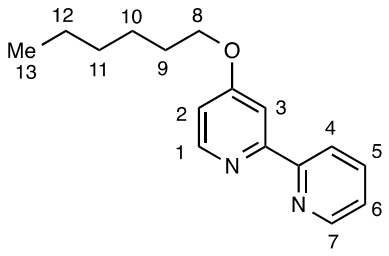
Hz, H_1) 6.96 (1H, d, J = 2.2 Hz, H_3) 6.74 (1H, dd, J = 5.7, 2.2 Hz, H_2), 3.97 (2H, t, J = 6.6 Hz, H_4), 1.77 (2H, qn, J = 6.8 Hz, H_5), 1.43 (2H, qn, J = 6.8 Hz, H_6), 1.37-1.28 (4H, m, H_7 and H_8), 0.89 (3H, t, J = 6.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.32, 150.51, 142.92, 113.59, 110.46, 68.52, 31.37, 28.66, 25.46, 22.49, 13.94. The spectroscopic data is in agreement with a reported synthesis.[7] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 258.0, $C_{11}H_{17}BrNO^+$ requires 258.0.

2-Fluoro-4-(hexyloxy)pyridine (3ca)



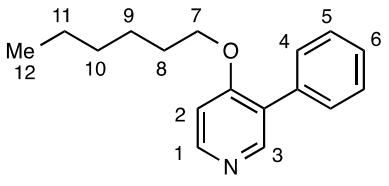
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (254 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 2.5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a yellow oil (67 mg, 0.34 mmol, 68% yield). IR ν_{max}/cm^{-1} (film): 2955, 1609, 1467, 1417, 1159; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (1H, d, J = 5.6 Hz, H_1) 6.68 (1H, dd, J = 5.7, 2.1 Hz, H_2) 6.35 (1H, d, J = 2.1 Hz, H_3) 3.99 (2H, t, J = 6.5 Hz, H_4) 1.79 (2H, qn, J = 6.7 Hz, H_5), 1.44 (2H, qn, J = 6.7 Hz, H_6) 1.38-1.28 (4H, m, H_7 and H_8), 0.90 (3H, t, J = 6.7 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.00 (d, J = 12.0 Hz), 165.31 (d, J = 235.0 Hz), 147.90 (d, J = 19.1 Hz), 109.38 (d, J = 3.8 Hz), 94.43 (d, J = 41.6 Hz), 68.69, 31.41, 28.69, 25.50, 22.51, 13.95; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -67.03; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 198.2, $C_{11}H_{17}FNO^+$ requires 198.1.

4-(Hexyloxy)-2,2'-bipyridine (3ea)



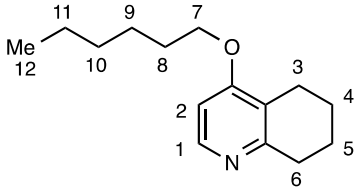
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), [2,2'-bipyridin]-4-yltriphenylphosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (basic alumina, gradient elution: 5% EtOAc in hexanes to 20% EtOAc in hexanes) afforded the title compound as a pink oil (72 mg, 0.28 mmol, 56% yield). IR ν_{max}/cm^{-1} (film): 3058, 2929, 1582, 1458, 1302, 1209, 793; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, d, J = 4.7 Hz, H_7), 8.43 (1H, d, J = 5.7 Hz, H_1), 8.36 (1H, d, J = 7.7 Hz, H_4), 7.92 (1H, d, J = 2.4 Hz, H_3), 7.76 (1H, t, J = 7.7 Hz, H_5), 7.25 (1H, dd, J = 7.7, 4.7 Hz, H_6), 6.78 (1H, dd, J = 5.7, 2.4 Hz, H_2), 4.08 (2H, t, J = 6.6 Hz, H_8), 1.78 (2H, qn, J = 6.8 Hz, H_9), 1.48-1.25 (6H, m, H_{10}, H_{11}, and H_{12}), 0.87 (3H, t, J = 6.5 Hz, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.17, 157.86, 156.03, 150.18, 148.97, 136.79, 123.69, 121.18, 111.09, 106.56, 68.01, 31.44, 28.88, 25.56, 22.52, 13.95; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 257.2, $C_{16}H_{20}N_2O^+$ requires 257.2.

4-(Hexyloxy)-3-phenylpyridine (3fa)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), triphenyl(3-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a yellow oil (92 mg, 0.36 mmol, 72% yield). IR ν_{max}/cm^{-1} (film): 3055, 2930, 1584, 1280, 1007, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50-8.38 (2H, m, H_1 and H_3), 7.53 (2H, d, J = 7.5 Hz, H_4), 7.42 (2H, t, J = 7.5 Hz, H_5), 7.35 (1H, t, J = 7.5 Hz, H_6), 6.86 (1H, d, J = 5.5 Hz, H_2), 4.03 (2H, t, J = 6.5 Hz, H_7), 1.75 (2H, qn, J = 6.5 Hz, H_8), 1.41 (2H, qn, J = 6.7 Hz, H_9), 1.35-1.24 (4H, m, H_{10} and H_{11}), 0.88 (3H, t, J = 6.7, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.89, 150.82, 150.28, 134.91, 129.42, 128.04, 127.42, 126.38, 107.07, 68.09, 31.27, 28.61, 25.52, 22.44, 13.86; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 256.2, $C_{17}H_{22}NO^+$ requires 256.2.

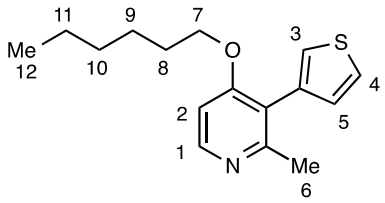
4-(Hexyloxy)-5,6,7,8-tetrahydroquinoline (3ga)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), triphenyl(5,6,7,8-tetrahydroquinolin-4-yl)phosphonium trifluoromethanesulfonate (272 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (neutralized silica gel: 20% EtOAc in hexanes) afforded the title compound as a yellow oil (93 mg, 0.40 mmol, 79% yield). IR ν_{max}/cm^{-1} (film): 2929, 2870, 1574, 1463, 1289, 1105; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (1H, d, J = 5.5 Hz, H_1), 6.51 (1H, d,

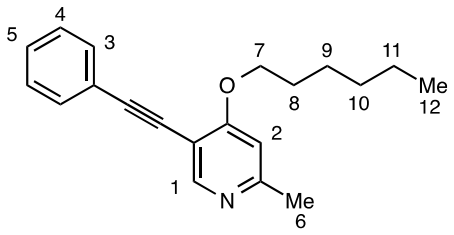
J = 5.5 Hz, H_2), 3.94 (2H, t, J = 6.4 Hz, H_7), 2.83 (2H, t, J = 6.1 Hz, H_6), 2.60 (2H, t, J = 6.1 Hz, H_3), 1.88-1.67 (6H, m, H_4, H_5, and H_8), 1.43 (2H, qn, J = 6.7 Hz, H_9), 1.37-1.24 (4H, m, H_{10} and H_{11}), 0.88 (3H, t, J = 6.7 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.82, 157.70, 147.66, 121.04, 103.70, 67.68, 32.45, 31.40, 28.86, 25.61, 22.73, 22.49, 22.17, 22.14, 13.90; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 234.2, $C_{15}H_{24}NO^+$ requires 234.2.

4-(Hexyloxy)-2-methyl-3-(thiophen-3-yl)pyridine (3ha)



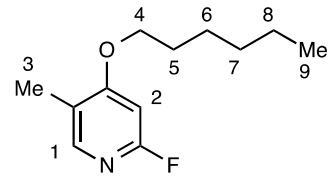
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-methyl-3-(thiophen-3-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (293 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (basic alumina, gradient elution: 15% EtOAc in hexanes to 25% EtOAc in hexanes) afforded the title compound as a yellow oil (100 mg, 0.36 mmol, 73% yield). IR ν_{max}/cm^{-1} (film): 2928, 1571, 1462, 1292, 1075, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (1H, d, J = 5.7 Hz, H_1), 7.33 (1H, dd, J = 5.0, 2.7 Hz, H_4), 7.15 (1H, d, J = 2.7 Hz, H_3), 7.02 (1H, d, J = 5.0 Hz, H_5), 6.68 (1H, d, J = 5.7 Hz, H_2), 3.92 (2H, t, J = 6.4 Hz, H_7), 2.38 (3H, s, H_6), 1.64 (2H, qn, J = 6.5 Hz, H_8), 1.34-1.17 (6H, m, H_9, H_{10}, and H_{11}), 0.84 (3H, t, J = 6.7 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.79, 157.75, 149.13, 134.76, 129.34, 124.26, 123.95, 120.93, 104.79, 68.03, 31.17, 28.53, 25.35, 23.36, 22.40, 13.85; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 276.2, $C_{16}H_{22}NOS^+$ requires 276.1.

4-(Hexyloxy)-2-methyl-5-(phenylethynyl)pyridine (3ia)



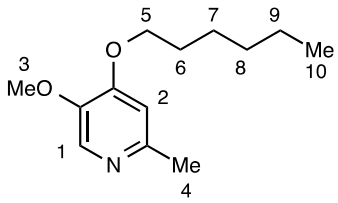
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-methyl-5-(phenylethynyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (302 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 15% EtOAc in hexanes) afforded the title compound as a white solid (91 mg, 0.31 mmol, 62% yield). mp 66–68 ºC; IR ν_{max}/cm^{-1} (film): 3055, 3035, 3019, 2954, 2930, 2871, 2855, 2731, 2594, 2224, 2161, 2050, 1979, 1966, 1947, 1893, 1822, 1802, 1667, 1544, 1426, 1325, 1237, 1147, 1126, 1068, 911, 768, 723, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (1H, s, H_1), 7.53 (2H, dd, J = 4.1, 7.0 Hz, H_4), 7.38–7.31 (3H, m, H_3 and H_5), 6.66 (1H, s, H_2), 4.08 (2H, t, J = 6.4 Hz, H_7), 2.55 (3H, s, H_6), 1.88 (2H, qn, 7.0 Hz, H_8), 1.54 (2H, qn, 7.0 Hz, H_9), 1.44–1.31 (4H, m, H_{10} and H_{11}), 0.90 (3H, t, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.25, 159.73, 152.67, 131.48, 128.24, 128.20, 123.31, 107.58, 106.12, 95.08, 82.79, 68.38, 31.43, 28.76, 25.54, 24.91, 22.54, 13.94; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 294.2, $C_{20}H_{24}NO^+$ requires 294.2.

2-Fluoro-4-(hexyloxy)-5-methylpyridine (3ja)



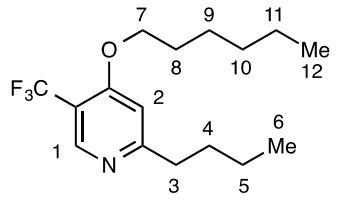
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 20 mg, 0.50 mmol), *n*-hexanol (63 μL, 0.50 mmol), (2-fluoro-5-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (261 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 2.5% EtOAc in hexanes) afforded the title compound as a white amorphous solid (64 mg, 0.30 mmol, 60% yield). mp 30-32 ºC; IR ν_{max}/cm^{-1} (film): 3073, 2944, 1610, 1493, 1332, 1160, 1026, 846; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (1H, s, H_1), 6.27 (1H, s, H_2), 3.98 (2H, t, J = 6.5 Hz, H_4), 2.10 (3H, s, H_3), 1.81 (2H, qn, J = 6.5 Hz, H_5), 1.54-1.27 (6H, m, H_6, H_7, and H_8), 0.90 (3H, t, J = 6.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.82 (d, J = 10.7 Hz), 163.77 (d, J = 233.5 Hz), 146.46 (d, J = 17.6 Hz), 120.38 (d, J = 4.6 Hz), 91.45 (d, J = 42.7 Hz), 68.47, 31.40, 28.66, 25.57, 22.51, 13.93, 12.59; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -69.11; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 212.2, $C_{12}H_{19}FNO^+$ requires 212.1.

4-(Hexyloxy)-5-methoxy-2-methylpyridine (3ka)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), a 7:1 mixture of (5-methoxy-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate and (3-methoxy-6-methylpyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (267 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then gradient elution: 40% EtOAc in hexanes to 50% EtOAc in hexanes) afforded the title compound as a tan amorphous solid (51 mg, 0.23 mmol, 46% yield). mp 41-42 ºC; IR ν_{max}/cm^{-1} (film): 3068, 3004, 2938, 1590, 1511, 1231, 1026; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.96 (1H, s, H_1), 6.61 (1H, s, H_2), 4.00 (2H, t, J = 7.2 Hz, H_5), 3.86 (3H, s, H_3), 2.43 (3H, s, H_4), 1.82 (2H, qn, J = 7.2 Hz, H_6), 1.43 (2H, qn, J = 7.1 Hz, H_7), 1.35-1.26 (4H, m, H_8 and H_9), 0.87 (3H, t, J = 7.0 Hz, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.99, 152.62 143.98, 133.25, 106.80, 68.47, 56.85, 31.42, 28.70, 25.48, 24.10, 22.47, 13.92; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 224.2, $C_{13}H_{22}NO_2^+$ requires 224.2.

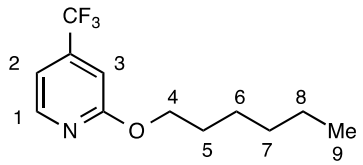
2-Butyl-4-(hexyloxy)-5-(trifluoromethyl)pyridine (3la)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-butyl-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (307 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: CH_2Cl_2) afforded the title

compound as a yellow oil (112 mg, 0.37 mmol, 74% yield). IR ν_{max}/cm^{-1} (film): 2957, 2861, 1603, 1325, 1129, 1043; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (1H, s, H_1), 6.71 (1H, s, H_2), 4.07 (2H, t, J = 6.5 Hz, H_7), 2.76 (2H, t, J = 7.6 Hz, H_3), 1.81 (2H, qn, J = 6.5 Hz, H_8), 1.69 (2H, qn, J = 7.7 Hz, H_4), 1.50-1.25 (8H, m, H_5, H_9, H_{10}, and H_{11}), 0.95-0.85 (6H, m, H_6 and H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.62, 163.29, 147.39 (q, J = 5.8 Hz), 123.42 (q, J = 272.4 Hz), 113.06 (q, J = 31.3 Hz), 106.25, 68.64, 38.59, 31.74, 31.28, 28.57, 25.33, 22.46, 22.44, 13.86, 13.83; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -62.29; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 304.2, $C_{16}H_{25}F_3NO^+$ requires 304.2.

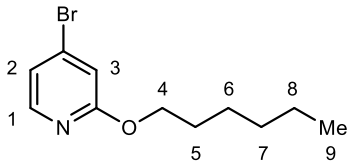
2-(Hexyloxy)-4-(trifluoromethyl)pyridine (3ma)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), triphenyl(4-(trifluoromethyl)pyridin-2-yl)phosphonium trifluoromethanesulfonate (279 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 2.5% EtOAc in hexanes) afforded the title compound as a yellow oil (79 mg, 0.32 mmol, 64% yield). IR ν_{max}/cm^{-1} (film): 2932, 1571, 1423, 1375, 1335, 1171, 1138; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (1H, d, J = 5.3 Hz, H_1), 7.02 (1H, d, J = 5.3 Hz, H_2), 6.94 (1H, s, H_3), 4.32 (2H, t, J = 6.6 Hz, H_4), 1.77 (2H, qn, J = 6.7 Hz, H_5), 1.44 (2H, qn, J = 6.7 Hz, H_6), 1.38-1.28 (4H, m, H_7 and H_8), 0.90 (3H, t, J = 6.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.48, 148.26, 140.76 (q, J = 33.6 Hz), 122.72 (q, J = 273.1 Hz), 111.88 (q, J = 3.1 Hz), 107.76 (q, J = 4.0 Hz), 66.77, 31.57, 28.88, 25.70, 22.60, 13.98; ^{19}F NMR

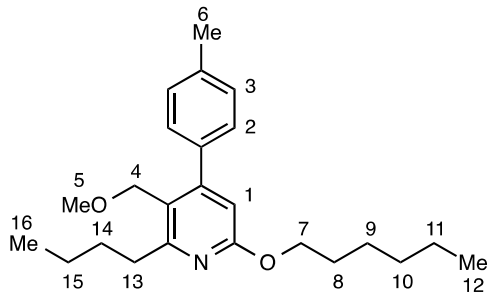
(365 MHz, $CDCl_3$) δ: -65.16; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 248.1, $C_{12}H_{17}F_3NO^+$ requires 248.1.

4-bromo-2-(hexyloxy)pyridine (3na)



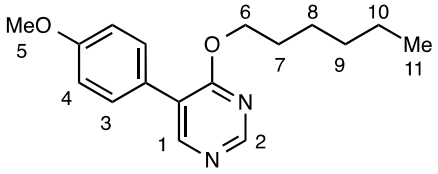
Prepared according to general procedure B (except that the reaction was allowed to stir for 14 hours after the addition of the phosphonium salt and CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 11 mg, 0.28 mmol), hexanol (35 μL, 0.28 mmol), (4-bromopyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (142 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel, gradient elution: 10% toluene in hexanes to 20% toluene in hexanes) to afford the title compound as a clear oil (33 mg, 0.13 mmol, 52% yield). IR ν_{max}/cm^{-1} (film): 2927, 1577, 1553, 1466, 1410, 1351, 1308, 1221, 1016, 982; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.96 (1H, d, J = 5.7 Hz, H_1), 6.99 (1H, dd, J = 5.7, 1.5 Hz, H_2), 6.93 (1H, d, J = 1.5 Hz, H_3), 4.26 (2H, t, J = 6.7 Hz, H_4), 1.75 (2H, qn, J = 7.3 Hz, H_5), 1.49-1.28 (6H, m, H_6, H_7, and H_8), 0.90 (3H, m, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) 164.69, 147.44, 133.69, 119.97, 114.26, 66.61, 31.54, 28.91, 25.67, 22.58, 14.01; m/z LRMS (ESI + APCI) found $[M+H]^+$ 258.1, $C_{11}H_{17}BrNO^+$ requires 258.0.

2-Butyl-6-(hexyloxy)-3-(methoxymethyl)-4-(*p*-tolyl)pyridine (3oa)



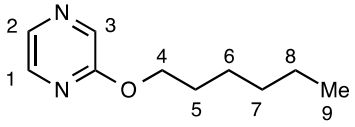
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), *n*-hexanol (47 μL, 0.38 mmol), (6-butyl-5-(methoxymethyl)-4-(*p*-tolyl)pyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (170 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel, gradient elution: 20% hexanes in CH_2Cl_2 to CH_2Cl_2) afforded the title compound as a yellow oil (69 mg, 0.19 mmol, 76 % yield). IR ν_{max}/cm^{-1} (film): 2927, 1594, 1342 1185, 1089, 821; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.32 (2H, d, J = 7.7 Hz, H_2), 7.23 (2H, d, J = 7.7 Hz, H_3), 6.47 (1H, s, H_1), 4.31 (2H, t, J = 6.7 Hz, H_7), 4.20 (2H, s, H_4), 3.32 (3H, s, H_5), 2.85 (2H, t, J = 7.8 Hz, H_{13}), 2.41 (3H, s, H_6), 1.84-1.72 (4H, m, H_{14} and H_8), 1.52-1.41 (4H, m, H_{15} and H_9), 1.40-1.29 (4H, m, H_{10} and H_{11}), 0.99 (3H, t, J = 7.4 Hz, H_{16}), 0.91 (3H, t, J = 7.0 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.64, 161.30, 154.16, 137.59, 136.74, 128.80, 128.71, 121.05, 107.82, 68.36, 65.95, 57.86, 34.45, 31.67, 31.64, 29.12, 25.76, 22.87, 22.61, 21.17, 14.09, 14.02; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 370.3, $C_{24}H_{36}NO_2^+$ requires 370.3.

4-(Hexyloxy)-5-(4-methoxyphenyl)pyrimidine (3pa)



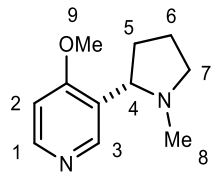
Prepared according to general procedure B (except that the reaction was allowed to stir for 30 hours after the addition of the phosphonium salt) using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (5-(4-methoxyphenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (298 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 20% EtOAc in hexanes) afforded the title compound as a yellow oil (85 mg, 0.30 mmol, 60% yield). IR ν_{max}/cm^{-1} (film): 3038, 2930, 1554, 1448, 1306, 1249, 995, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, s, H_2), 8.45 (1H, br s, H_1), 7.52-7.47 (2H, m, H_3), 6.99-6.93 (2H, m, H_4), 4.41 (2H, t, J = 6.7 Hz, H_6), 3.84 (3H, s, H_5), 1.77 (2H, qn, J = 6.8 Hz, H_7), 1.41 (2H, qn, J = 6.8 Hz, H_8), 1.36-1.27 (4H, m, H_9 and H_{10}), 0.87 (3H, t, J = 6.9 Hz, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.87, 159.57, 156.36, 155.36, 130.06, 125.29, 121.84, 113.87, 66.87, 55.22, 31.35, 28.53, 25.59, 22.46, 13.90; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 287.2, $C_{17}H_{23}N_2O_2^+$ requires 287.2.

2-(Hexyloxy)pyrazine (3qa)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), triphenyl(pyrazin-2-yl)phosphonium trifluoromethanesulfonate (245 mg, 0.5 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a yellow oil (70 mg, 0.39 mmol, 78% yield). IR ν_{max}/cm^{-1} (film): 3060, 2923, 1532, 1414, 1284, 1005; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (1H, br s, H_1), 8.10-7.97 (2H, br s, H_2 and H_3), 4.28 (2H, t, J = 6.7 Hz, H_4), 1.76 (2H, qn, J = 6.8 Hz, H_5), 1.42 (2H, qn, J = 6.8 Hz, H_6), 1.37-1.25 (4H, m, H_7 and H_8), 0.88 (3H, t, J = 6.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.46, 140.49, 136.18, 136.02, 66.40, 31.49, 28.74, 25.60, 22.54, 13.97. The spectroscopic data is in agreement with a reported synthesis.[8] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 181.2, $C_{10}H_{17}N_2O^+$ requires 181.1.

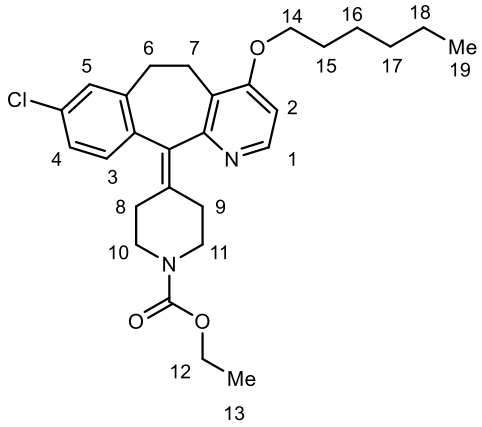
(*S*)-4-methoxy-3-(1-methylpyrrolidin-2-yl)pyridine (5)



Prepared according to general procedure B (except that CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), methanol (30 μL, 0.75 mmol), (*S*)-(3-(1-methylpyrrolidin-2-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (286 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then gradient elution: 1% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2) followed by a second flash

column (basic alumina: 2% MeOH in CH_2Cl_2) afforded the title compound as a tan amorphous solid (76 mg, 0.40 mmol, 79% yield). mp 73-75 ºC; IR ν_{max}/cm^{-1} (film): 3031, 2969, 2780, 1589, 1455, 1274, 1023, 805; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, br s, H_3), 8.34 (1H, br s, H_1), 6.70 (1H, d, J = 5.7 Hz, H_2), 3.81 (3H, s, H_9), 3.44 (1H, app t, J = 8.3 Hz, H_4), 3.19 (1H, app t, J = 8.5 Hz, H_7), 2.30-2.14 (5H, m, H_5, H_7, and H_8), 1.93-1.80 (1H, m, H_6), 1.80-1.69 (1H, m, H_6), 1.64-1.52 (1H, m, H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.51, 149.64, 148.92, 126.87, 105.58, 62.64, 56.96, 55.14, 40.73, 33.02, 22.66. The spectroscopic data is in agreement with a reported synthesis.[9] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 193.1, $C_{11}H_{17}N_2O^+$ requires 193.1.

Ethyl 4-(8-chloro-4-(hexyloxy)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (7)

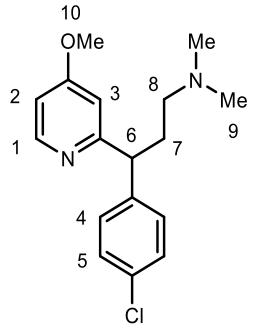


Prepared according to general procedure B (except that the reaction was allowed to stir for 15 hours after the addition of the phosphonium salt and CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), *n*-hexanol (47 μL, 0.38 mmol), (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium

trifluoromethanesulfonate (198 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then: 1% NEt_3, 50% CH_2Cl_2 in hexanes) followed by a second flash column (basic alumina, gradient elution: 30% EtOAc in hexanes to 50% EtOAc in hexanes)[8] afforded the title compound as a yellow oil (64 mg, 0.13 mmol, 53% yield). IR ν_{max}/cm^{-1} (film): 3010, 2929, 1688, 1567, 1435, 1230, 748 ^1H NMR (400 MHz, $CDCl_3$) δ: 8.27 (1H, d, J = 5.6 Hz, H_1), 7.18 (1H, s, H_5), 7.14-7.07 (2H, m, H_3 and H_4), 6.61 (1H, d, J = 5.6 Hz, H_2), 4.12 (2H, q, J = 7.1 Hz, H_{12}), 4.01-3.69 (4H, m, H_{10} or H_{11} and H_{12}), 3.40-3.28 (1H, m, H_6), 3.17-2.98 (3H, m, H_7 and H_{10} or H_{11}), 2.92-2.71 (2H, m, H_6 and H_7), 2.58-2.45 (1H, m, H_8 or H_9), 2.43-2.18 (3H, m, H_8 or H_9), 1.77 (2H, qn, J = 6.9 Hz, H_{15}), 1.50-1.28 (6H, m, H_{16}, H_{17}, and H_{18}), 1.27-1.17 (3H, m, H_{12}), 0.89 (3H, t, J = 6.9 Hz, H_{19}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.41, 156.51, 155.43, 147.69, 140.30, 138.79, 137.37, 133.98, 132.73, 129.73, 128.28, 126.05, 122.03, 104.98, 68.08, 61.22, 44.78, 44.70, 31.40, 30.70, 30.56, 29.64, 28.86, 25.67, 25.33, 22.49, 14.63, 13.94; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 483.3, $C_{28}H_{36}ClN_2O_3^+$ requires 483.2.

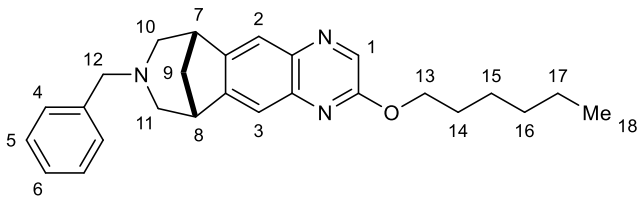
[8] To remove an impurity the product was dissolved in Et_2O (10 mL) and trifluoroacetic acid (0.5 mL) was added dropwise at 0 ºC and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with a saturated aqueous solution of sodium bicarbonate (10 mL). The organic layer was washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

3-(4-Chlorophenyl)-3-(4-methoxypyridin-2-yl)-*N*,*N*-dimethylpropan-1-amine (9)



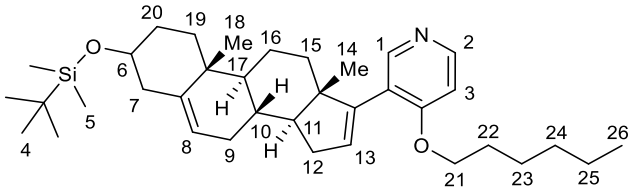
Prepared according to general procedure B (except that the reaction was allowed to stir for 18 hours after the addition of the phosphonium salt and CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), methanol (15 μL, 0.38 mmol), (2-(1-(4-chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (171 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then: 1% MeOH, 1% NEt_3 in CH_2Cl_2) followed by a second flash column (basic alumina: 2% MeOH in CH_2Cl_2) afforded the title compound as a tan oil (35 mg, 0.12 mmol, 46% yield). IR ν_{max}/cm^{-1} (film): 3011, 2940, 2768, 1593, 1567, 1488, 1304, 1037, 749; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.35 (1H, d, J = 5.6 Hz, H_1), 7.28-7.18 (4H, m, H_4 and H_5), 6.64 (1H, d, J = 2.4 Hz, H_3), 6.60 (1H, dd, J = 5.6, 2.4 Hz, H_2), 4.05-4.00 (1H, m, H_6), 3.75 (3H, s, H_{10}), 2.44-2.30 (1H, m, H_7), 2.21-2.06 (9H, m, H_7, H_8, and H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.01, 164.65, 150.60, 142.03, 132.15, 129.33, 128.54, 108.86, 107.51, 57.59, 54.98, 50.60, 45.36, 32.69; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 305.2, $C_{17}H_{22}ClN_2O^+$ requires 305.1.

(*rac*)-2-(Hexyloxy)-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxaline (11)



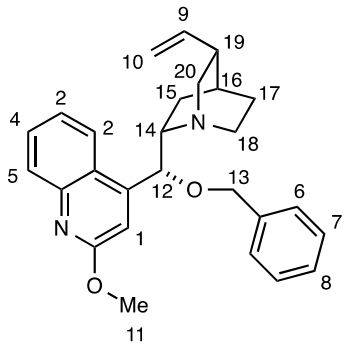
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 11 mg, 0.28 mmol), *n*-hexanol (35 μL, 0.28 mmol), triphenyl((*rac*)-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxalin-2-yl)phosphonium trifluoromethanesulfonate (130 mg, 0.18 mmol) and THF (0.4 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a tan oil (18 mg, 0.045 mmol, 25% yield).; IR ν_{max}/cm^{-1} (film): 3026, 2950, 1570, 1473, 1345, 1300, 1204; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (1H, s, H_1), 7.69 (1H, s, H_2) 7.56 (1H,s, H_3), 7.15-7.09 (3H, m, H_5 and H_6), 6.90-6.82 (2H, m, H_4), 4.47 (2H, t, J = 6.8 Hz, H_{13}), 3.48 (2H, s, H_{12}) 3.32-3.25 (2H, br s, H_7 and H_8), 2.95 (2H, m, H_{10} or H_{11}), 2.53 (2H, m, H_{10} or H_{11}), 2.37-2.27 (1H, m, H_9), 1.91-1.78 (3H, m, H_9 and H_{14}), 1.57-1.45 (2H, m, H_{15}), 1.44-1.32 (4H, m, H_{16} and H_{17}), 0.93 (3H, t, J = 7.0 Hz, H_{18}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.19, 150.56, 146.56, 140.35, 138.59, 138.38, 137.42, 128.34, 127.99, 126.58, 120.32, 118.83, 66.29, 61.59, 57.31, 57.12, 43.51, 41.38, 40.98, 31.58, 28.83, 25.75, 22.61, 14.06; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 402.2, $C_{26}H_{32}N_3O^+$ requires 402.3.

3-((8*R*,9*S*,10*R*,13*S*,14*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)-4-(hexyloxy)pyridine (13)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), *n*-hexanol (47 μL, 0.38 mmol), (3-((8*R*,9*S*,10*R*,13*S*,14*S*)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (219 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel, gradient elution: 30% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a white solid (82 mg, 0.15 mmol, 60% yield). mp 59-64 ºC; IR ν_{max}/cm^{-1} (film): 2928, 1577, 1496, 1382, 1279, 1250, 1077, 1022, 888; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40-8.15 (2H, m), 6.76 (1H, d, *J* = 5.6 Hz), 5.89-5.84 (1H, dd, *J* = 3.0, 1.5 Hz), 5.38-5.32 (1H, m), 3.98 (2H, t, *J* = 6.6 Hz), 3.49 (1H, m), 2.34-2.14 (3H, m), 2.12-1.99 (2H, m), 1.85-1.27 (18H, m), 1.12-0.81 (20H, m), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.00, 150.04, 149.49, 148.60, 141.88, 130.91, 123.01, 120.90, 106.78, 72.57, 68.01, 57.21, 50.59, 48.61, 42.83, 37.29, 36.79, 34.99, 32.14, 32.05, 31.63, 31.38, 30.71, 28.74, 25.92, 25.66, 22.56, 20.84, 19.35, 18.24, 16.12, 13.98, -4.60; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 564.4, $C_{36}H_{58}NO_2Si^+$ requires 564.4.

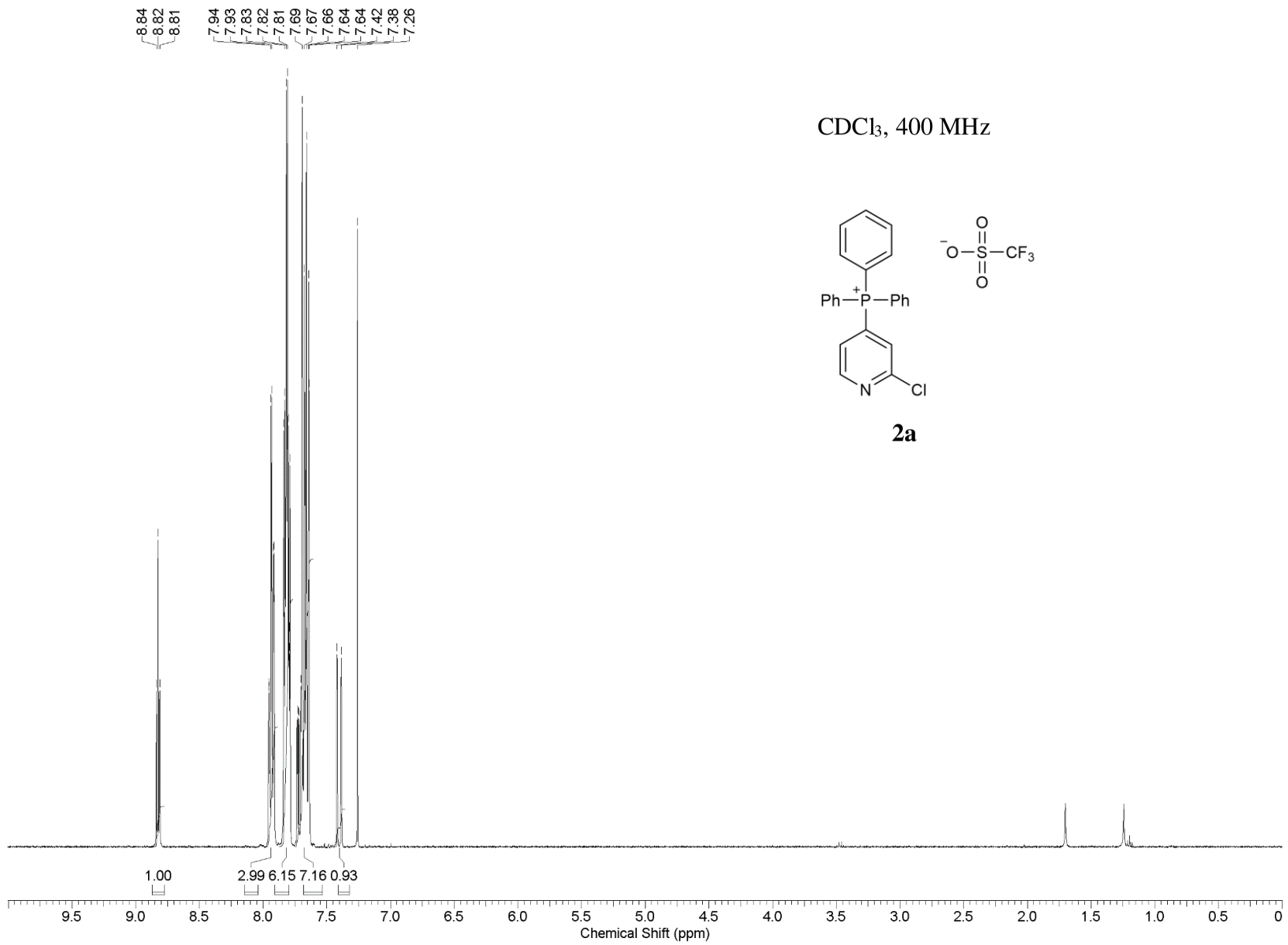
(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(Benzyloxy)(2-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (15)



Prepared according to general procedure B (except that the reaction was allowed to stir for 11 hours after the addition of the phosphonium salt and CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), methanol (15 μL, 0.38 mmol), (4-((*R*)-(benzyloxy)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (199 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then: 1% NEt_3, 50% CH_2Cl_2 in hexanes) afforded the title compound as a pale yellow oil (60 mg, 0.14 mmol, 58% yield). IR ν_{max}/cm^{-1} (film): 3065, 2938, 1609, 1382, 1338, 1236, 1045, 754; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.00 (1H, d, J = 8.0 Hz, H_2), 7.91 (1H, d, J = 8.2 Hz, H_5), 7.64 (1H, t, J = 7.5 Hz, H_4), 7.45-7.27 (6H, m , H_6, H_7, H_8 and H_3), 7.06 (1H s, H_1), 5.83-5.64 (1H, m, H_9), 5.31-5.15 (1H, br s, H_{12}), 5.00-4.85 (2H, m, H_{10}), 4.50 (1H, d, J = 11.3 Hz, H_{13}), 4.40 (1H, d, J = 11.3 Hz, H_{13}), 4.07 (3H, s, H_{11}), 3.45-3.31 (1H, m , H_{18}), 3.18-3.03 (2H, m, H_{20} and H_{14}), 2.72-2.55 (2H, m, H_{18} and H_{20}), 2.30-2.18 (1H, m, H_{19}), 1.89-1.40 (5H, m, H_{15}, H_{16}, and H_{17}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.30, 148.70, 147.35, 141.69, 137.83, 129.26, 128.38, 128.17, 127.65, 127.61, 124.10, 123.38, 123.23, 114.29, 110.34, 80.78, 71.23, 60.30, 56.94, 53.24,

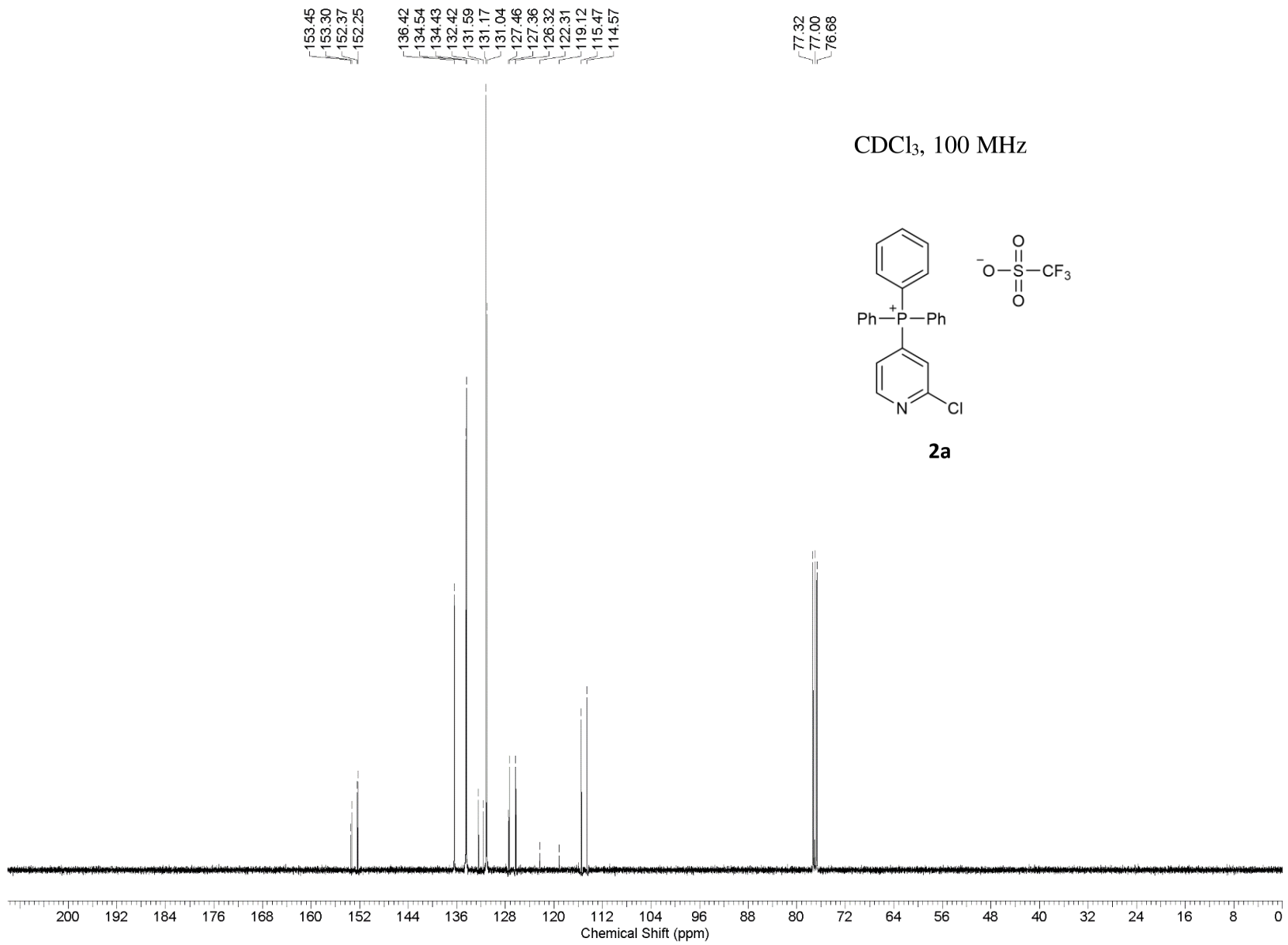
43.17, 39.89, 27.89, 27.55, 22.07; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 415.3, $C_{27}H_{31}N_2O_2^+$ requires 415.2.

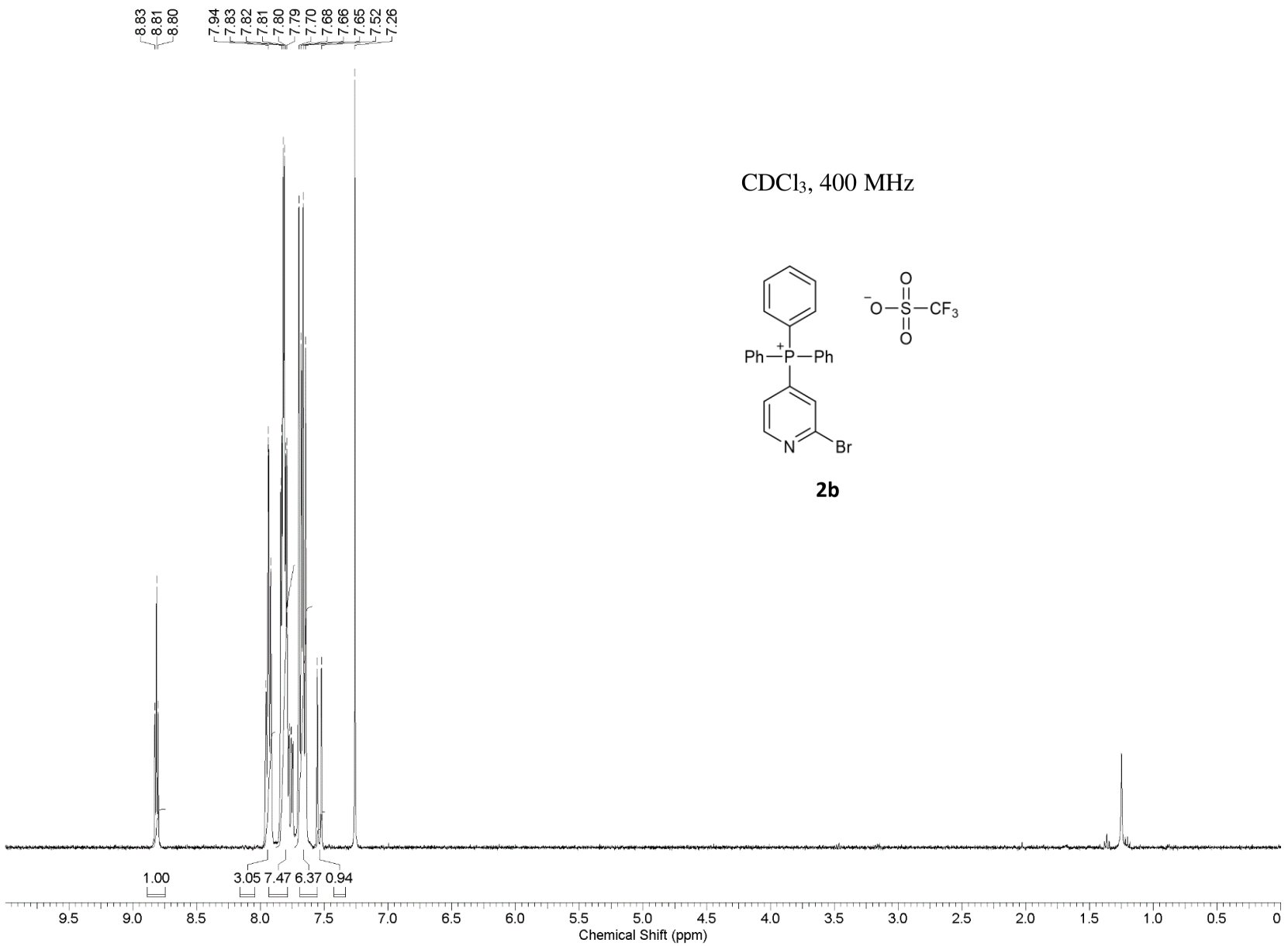
A 1.4 Spectra

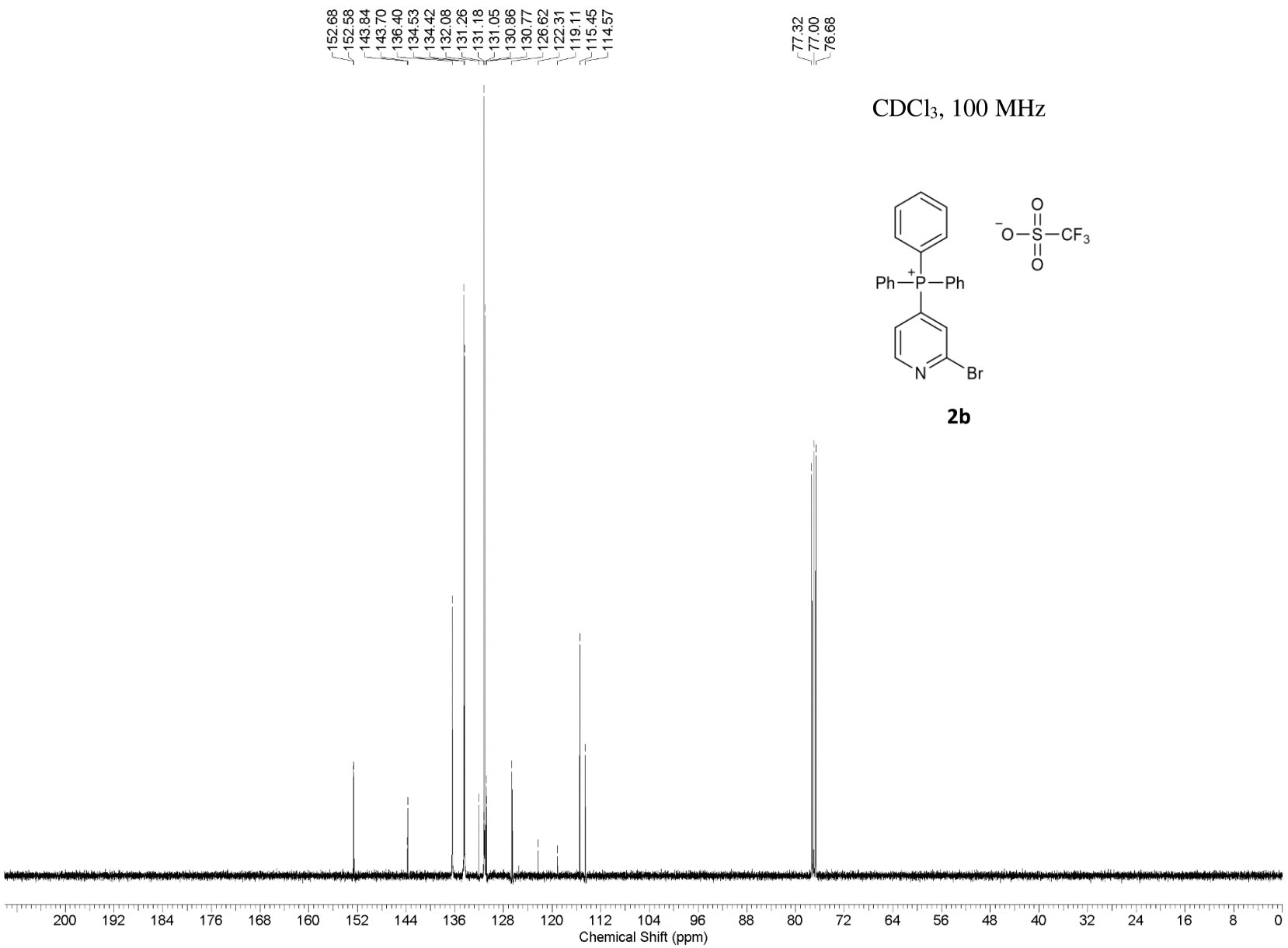


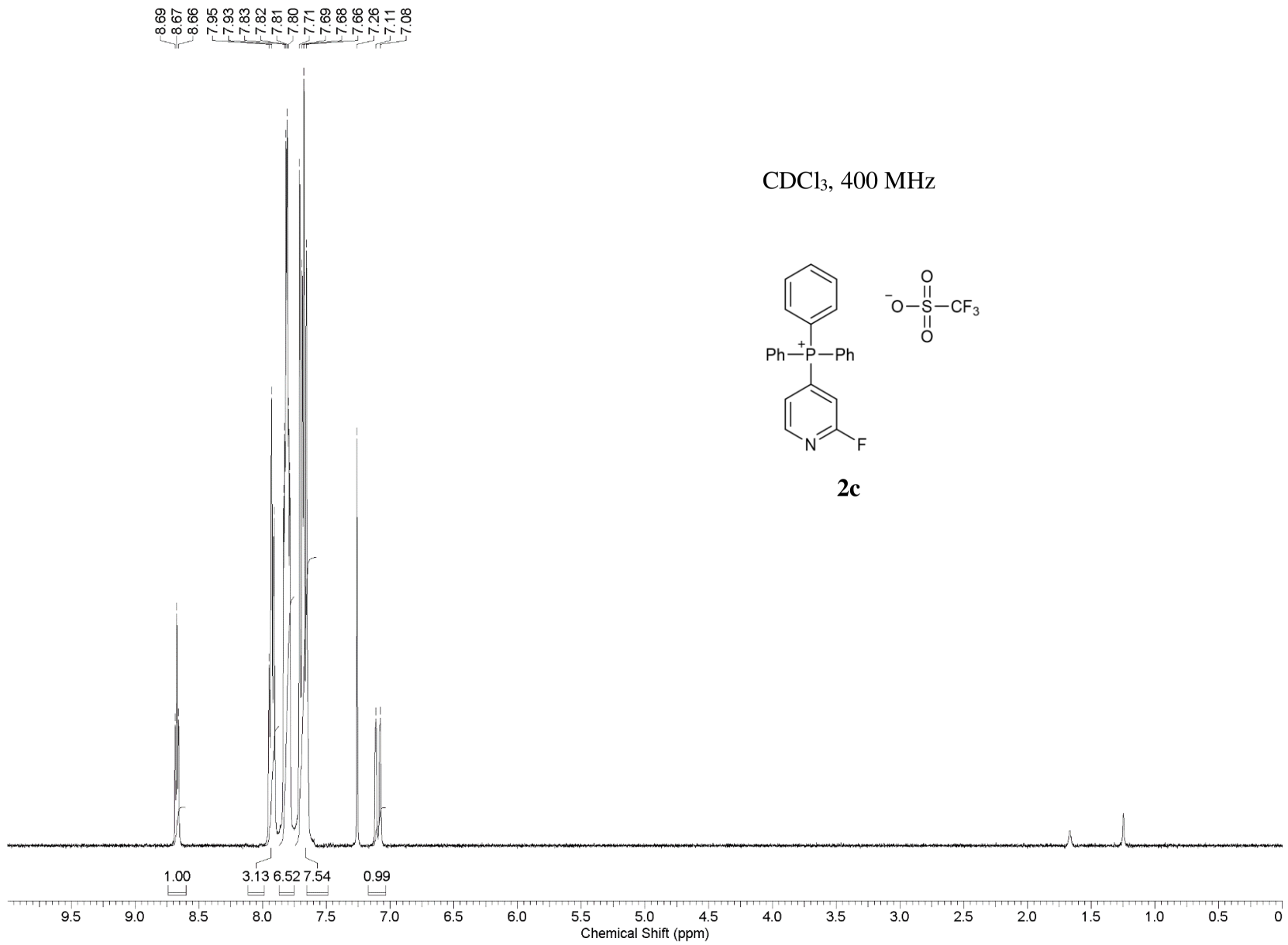
$CDCl_3$, 400 MHz

2a


153.45
153.30
152.37
152.25
136.42
134.54
134.43
132.42
131.59
131.17
131.04
127.46
127.36
126.32
122.31
119.12
115.47
114.57
77.32
77.00
76.68
CDCl3, 100 MHz
Ph
P
Ph
O
S
CF3
N
Cl
2a
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

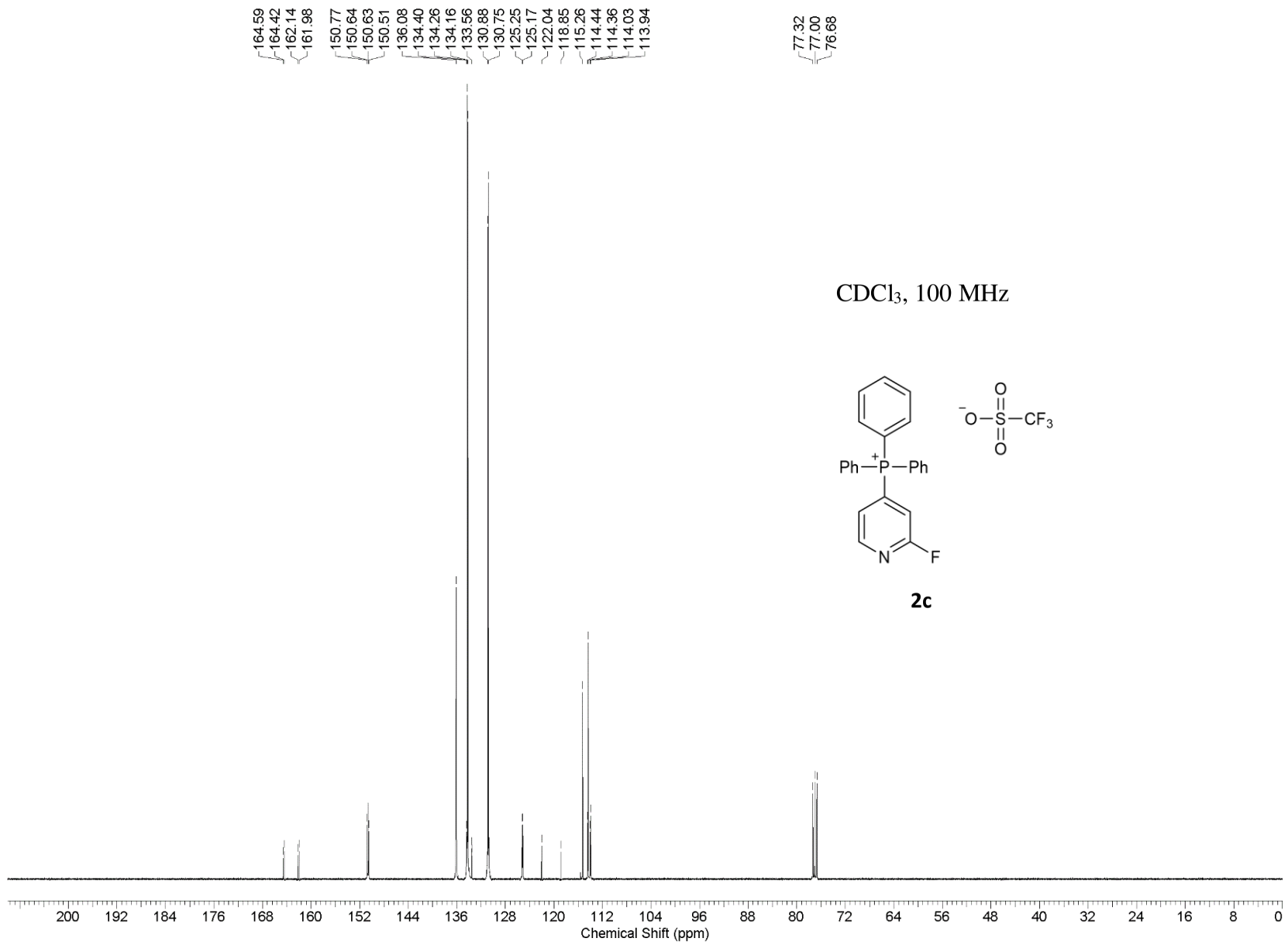

8.83
8.81
8.80
7.94
7.83
7.82
7.81
7.80
7.79
7.70
7.68
7.66
7.65
7.52
7.26
CDCl3, 400 MHz
Ph—P—Ph
N
Br
O—S—CF3
2b
1.00
3.05
7.47
6.37
0.94
Chemical Shift (ppm)

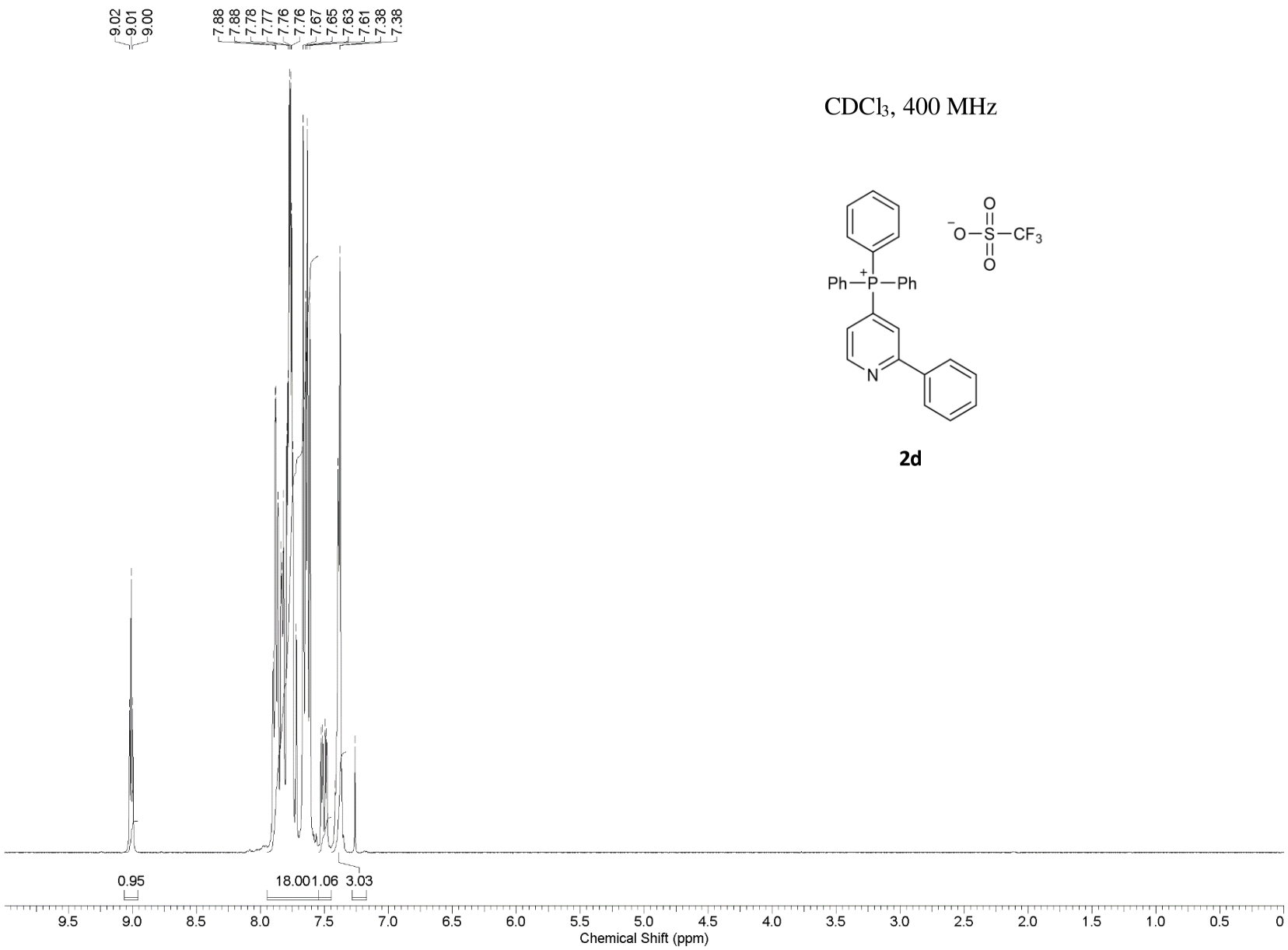

152.68
152.58
143.84
143.70
136.40
134.53
134.42
132.08
131.26
131.18
131.05
130.86
130.77
126.62
122.31
119.11
115.45
114.57
77.32
77.00
76.68
CDCl3, 100 MHz
Ph—P—Ph
O—S—CF3
N
Br
2b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



$CDCl_3$, 400 MHz

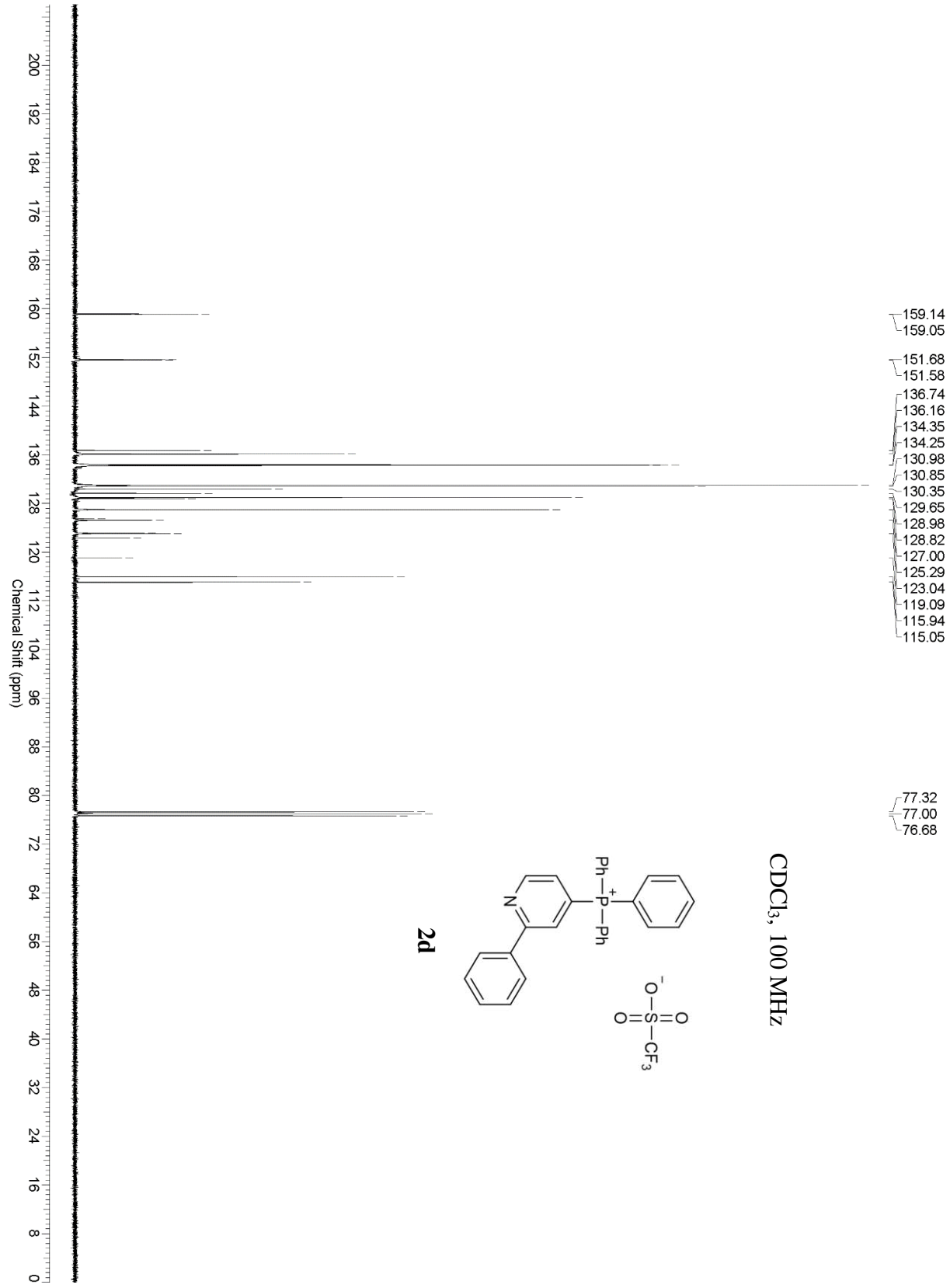
2c


164.59
164.42
162.14
161.98
150.77
150.64
150.63
150.51
136.08
134.40
134.26
134.16
133.56
130.88
130.75
125.25
125.17
122.04
118.85
115.26
114.44
114.36
114.03
113.94
77.32
77.00
76.68
CDCl3, 100 MHz
Ph
P
Ph
N
F
O
S
CF3
2c
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



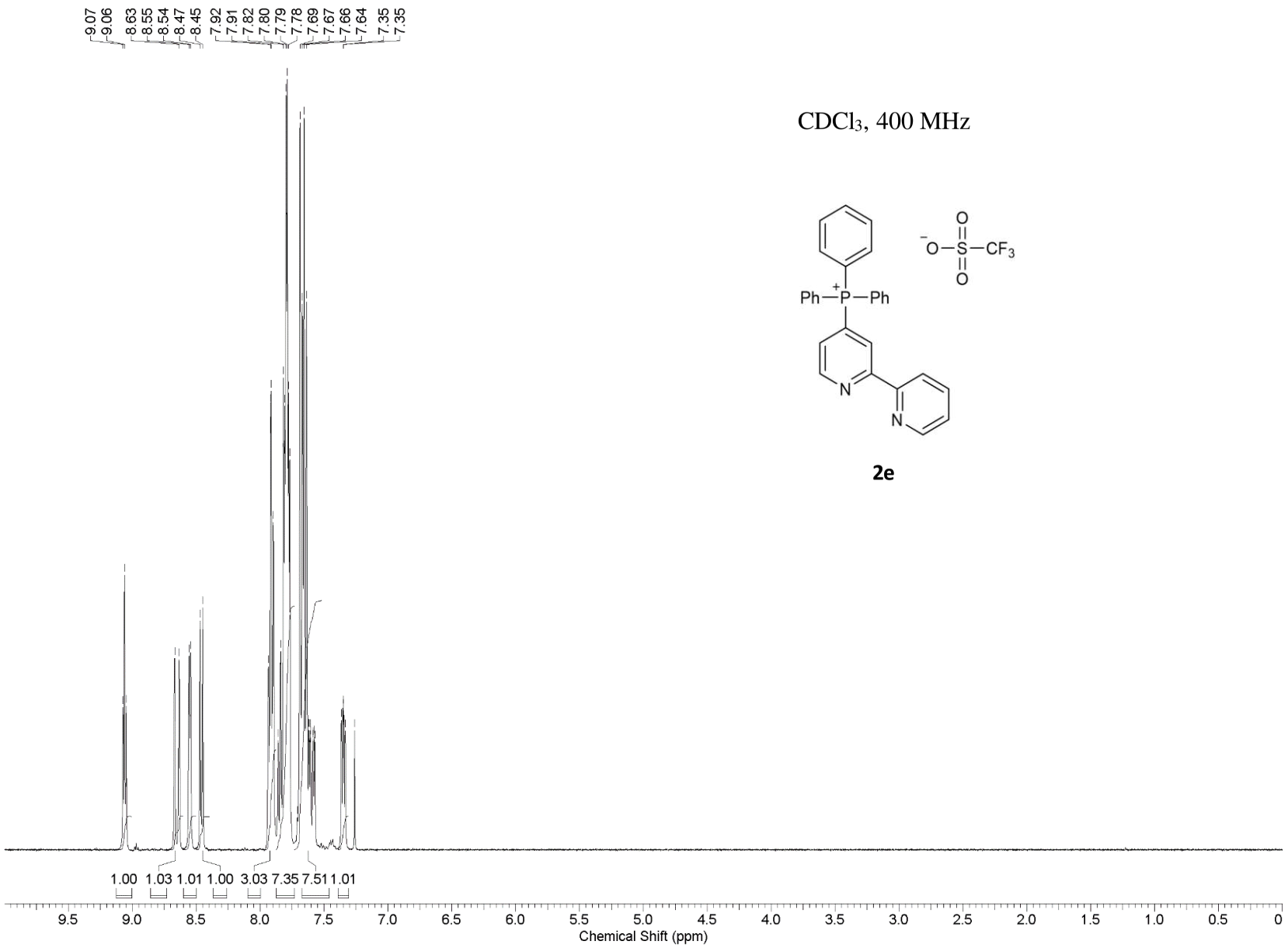
$CDCl_3$, 400 MHz

2d



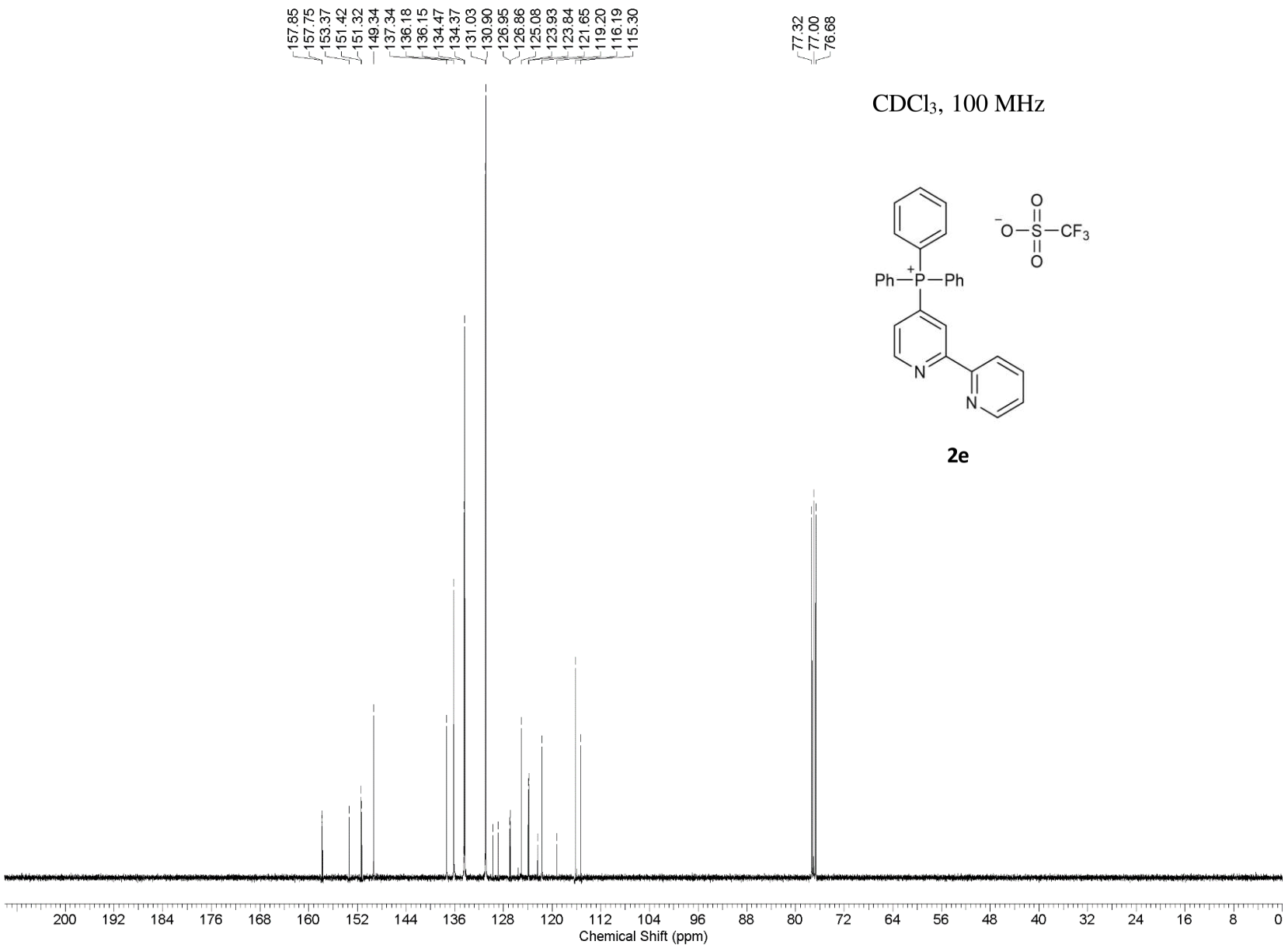
2d

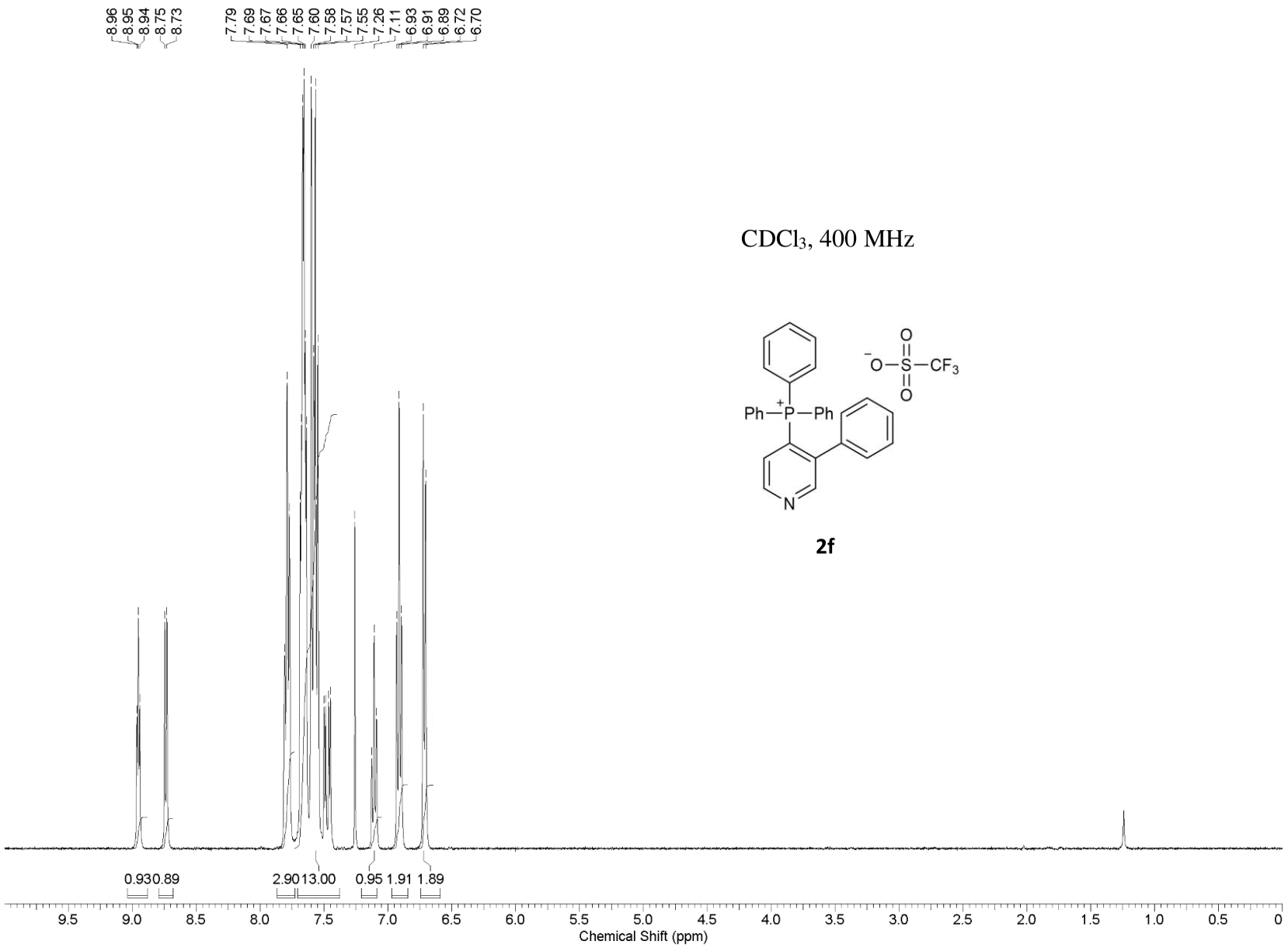
$CDCl_3$, 100 MHz



$CDCl_3$, 400 MHz

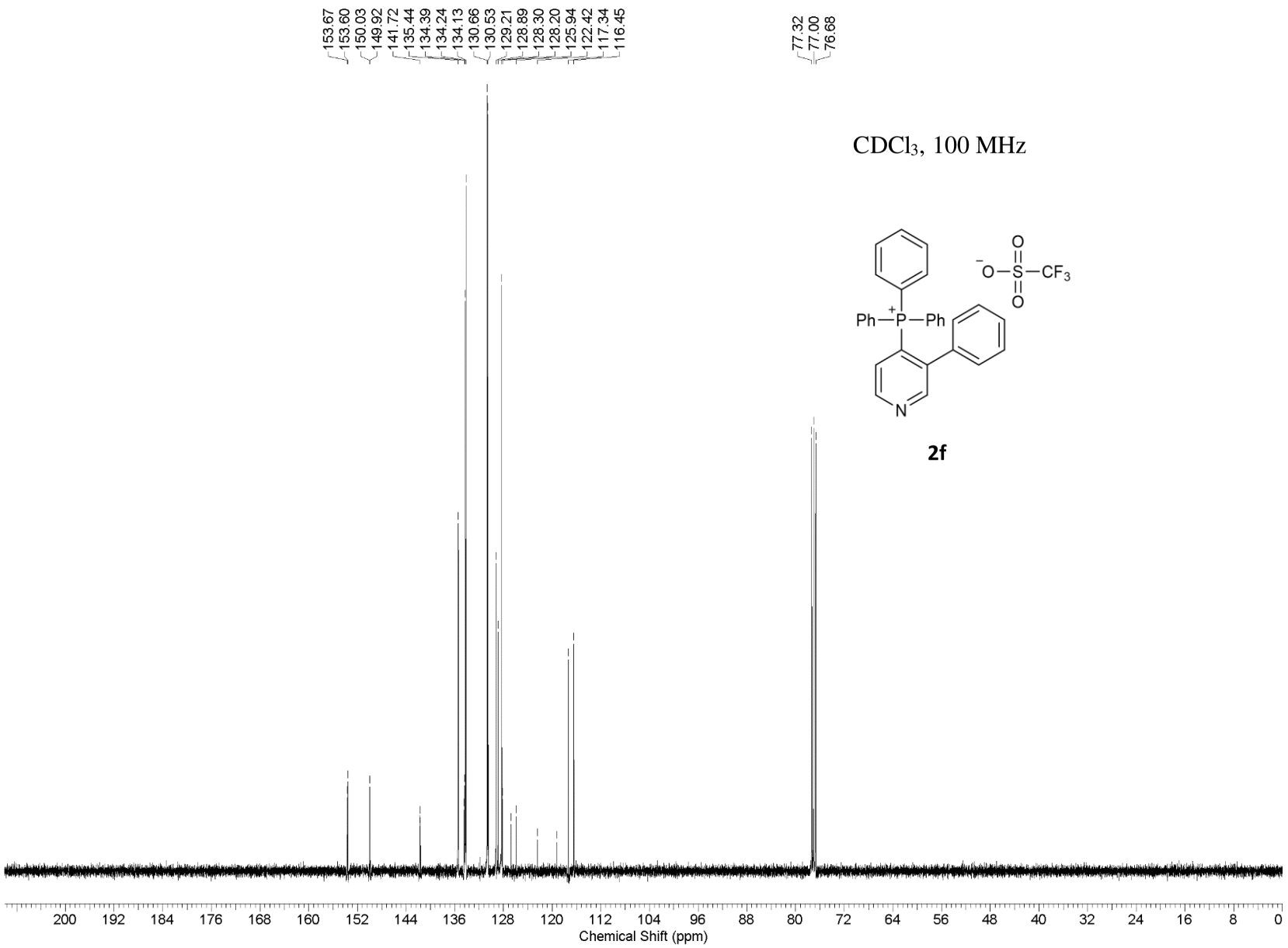
2e


157.85
157.75
153.37
151.42
151.32
149.34
137.34
136.18
136.15
134.47
134.37
131.03
130.90
126.95
126.86
125.08
123.93
123.84
121.65
119.20
116.19
115.30
77.32
77.00
76.68
CDCl3, 100 MHz
Ph—P—Ph
O—S—CF3
N
N
2e
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

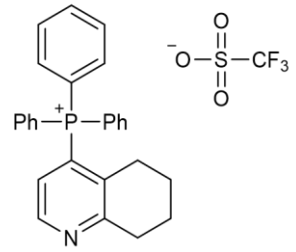


$CDCl_3$, 400 MHz

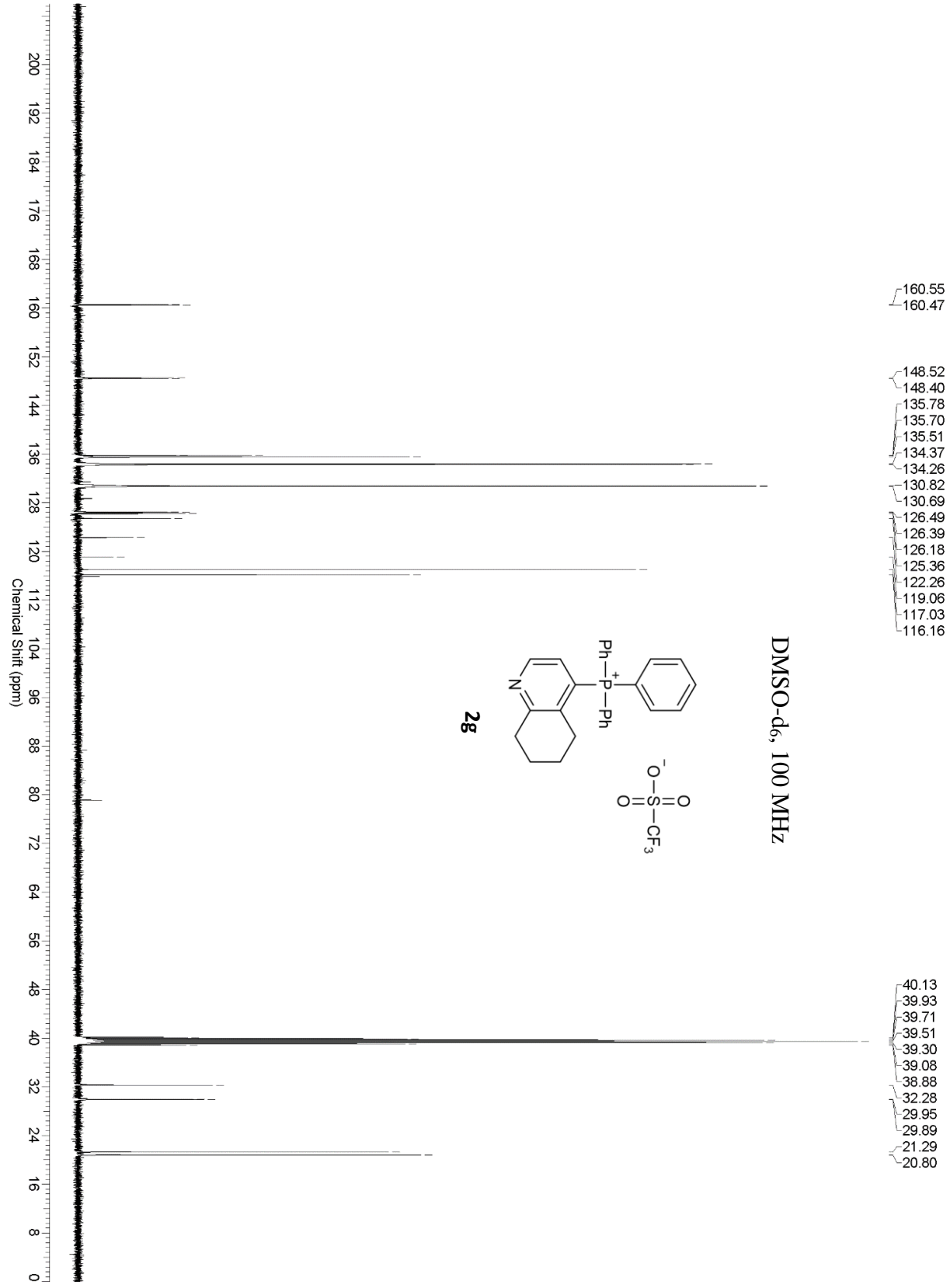
2f

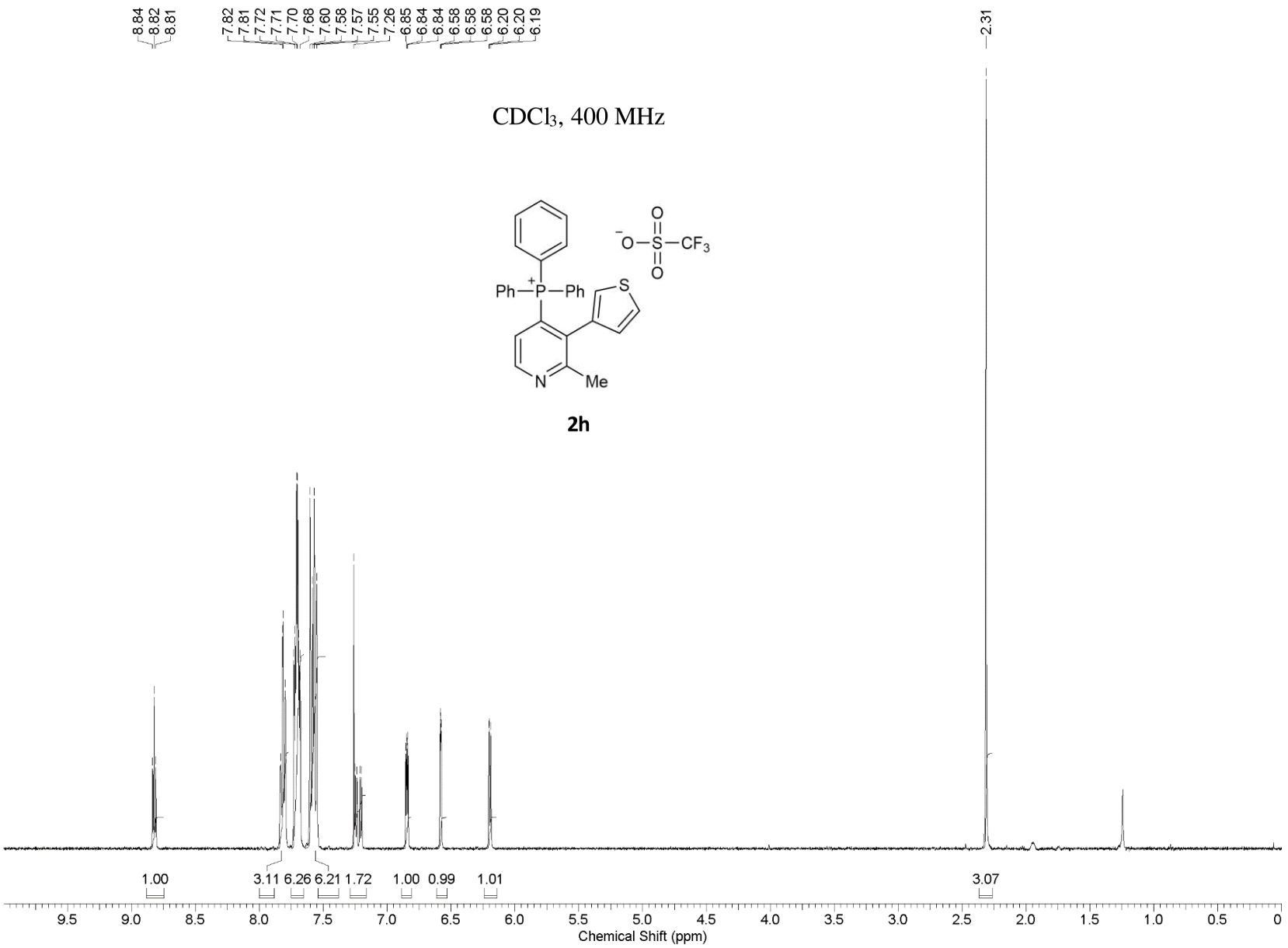

153.67
153.60
150.03
149.92
141.72
135.44
134.39
134.24
134.13
130.66
130.53
129.21
128.89
128.30
128.20
125.94
122.42
117.34
116.45
77.32
77.00
76.68
CDCl3, 100 MHz
Ph—P—Ph
O—S—CF3
N
2f
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

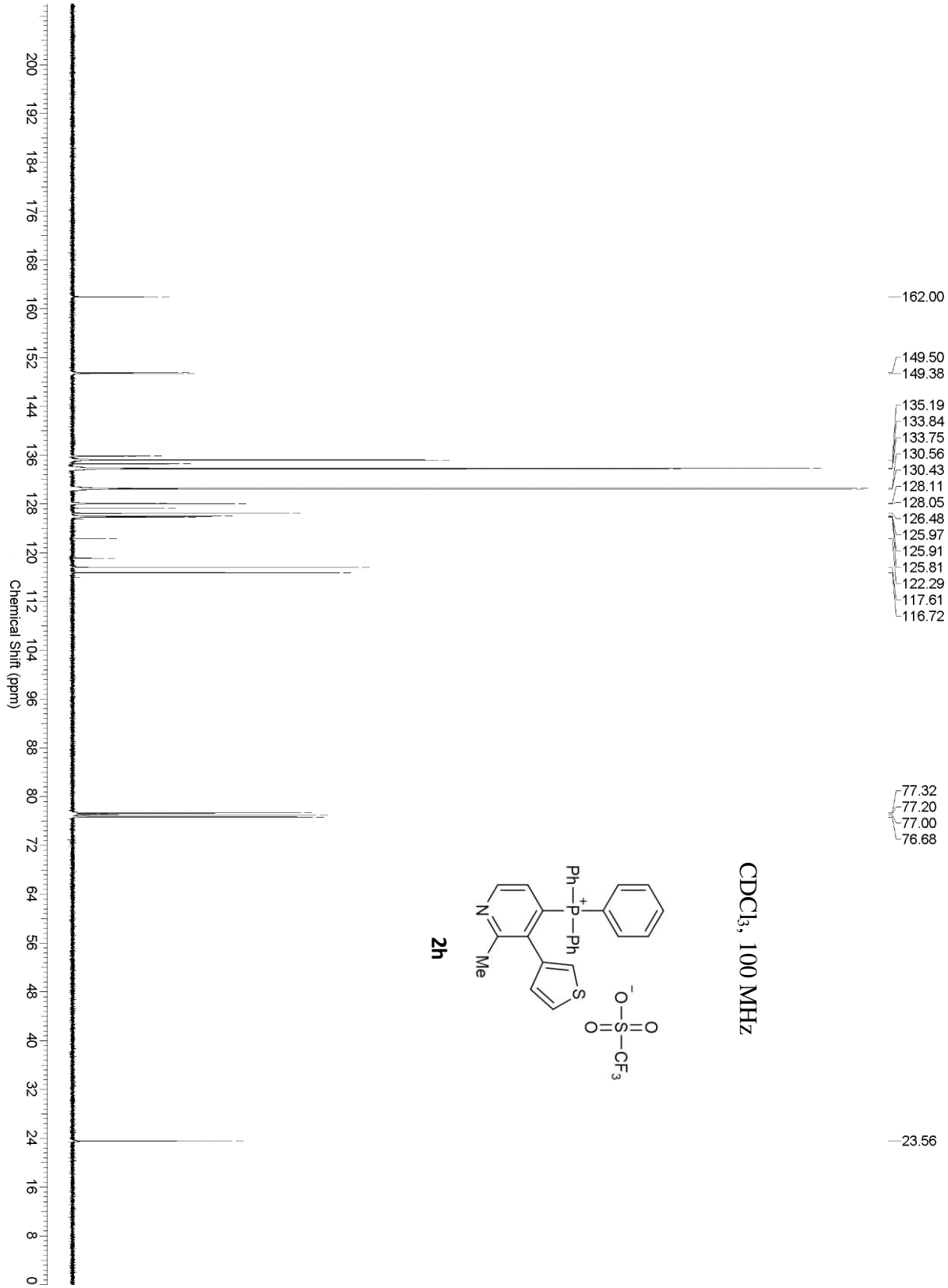
DMSO-d_6, 400 MHz

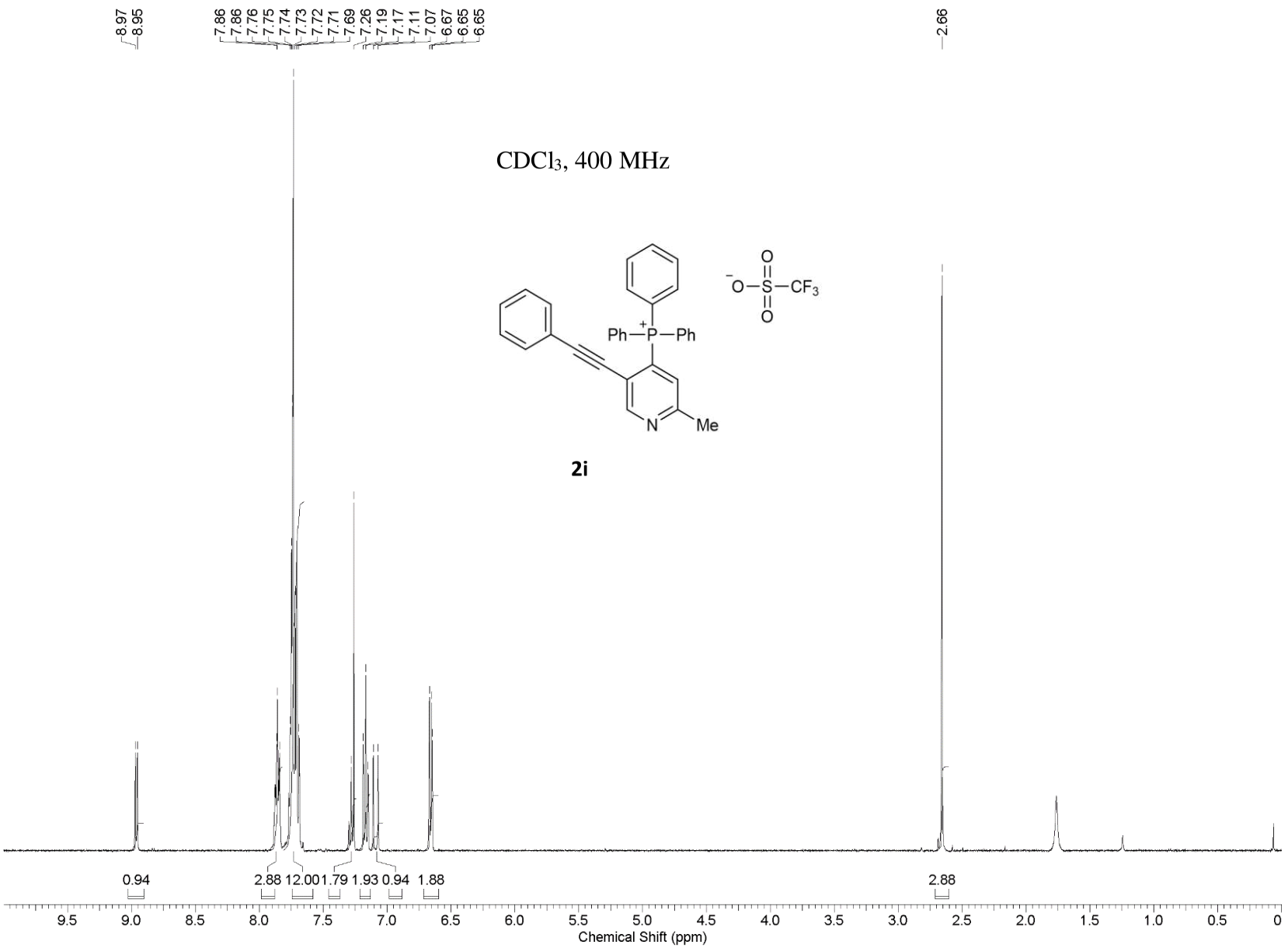


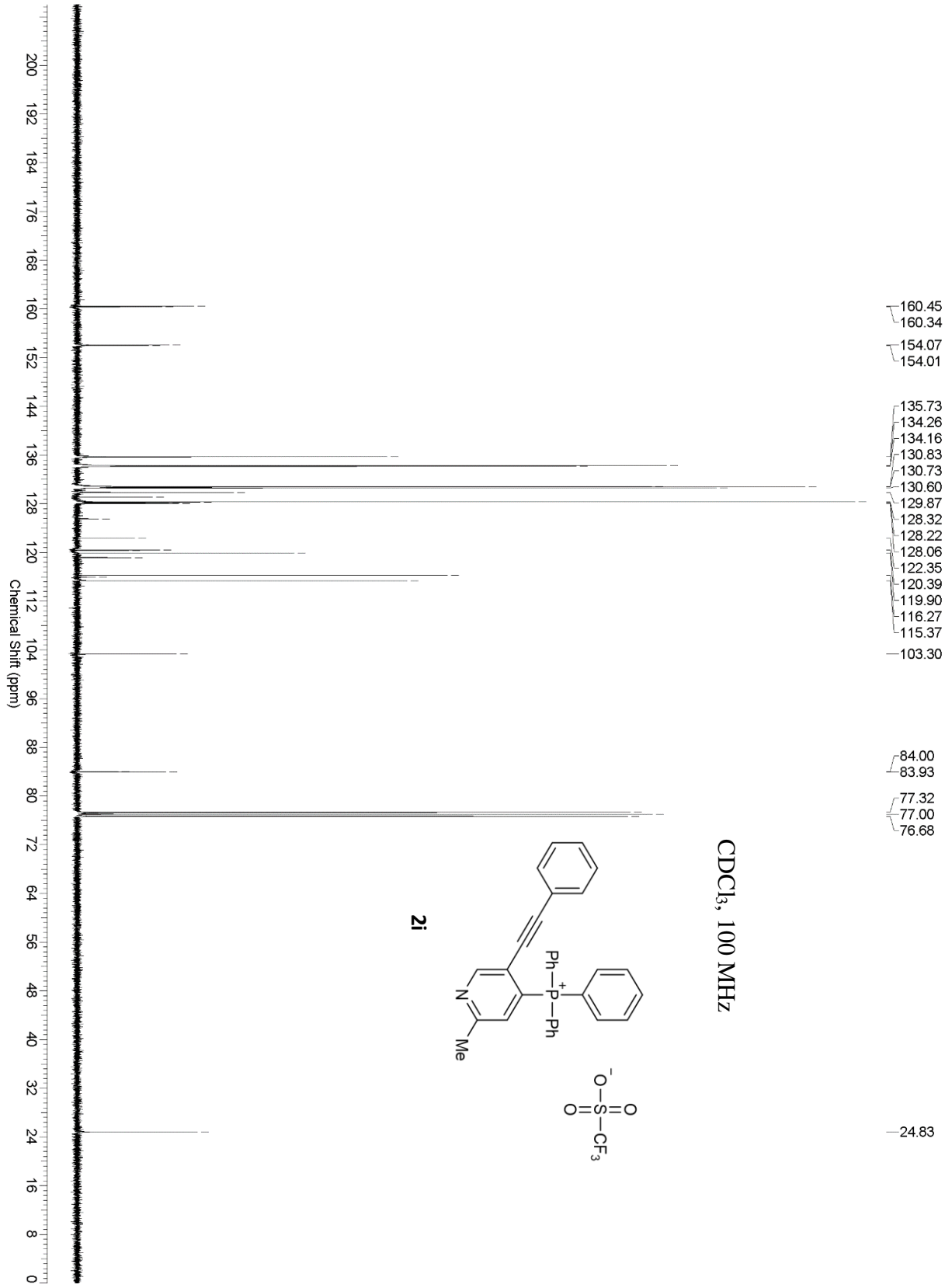
2g

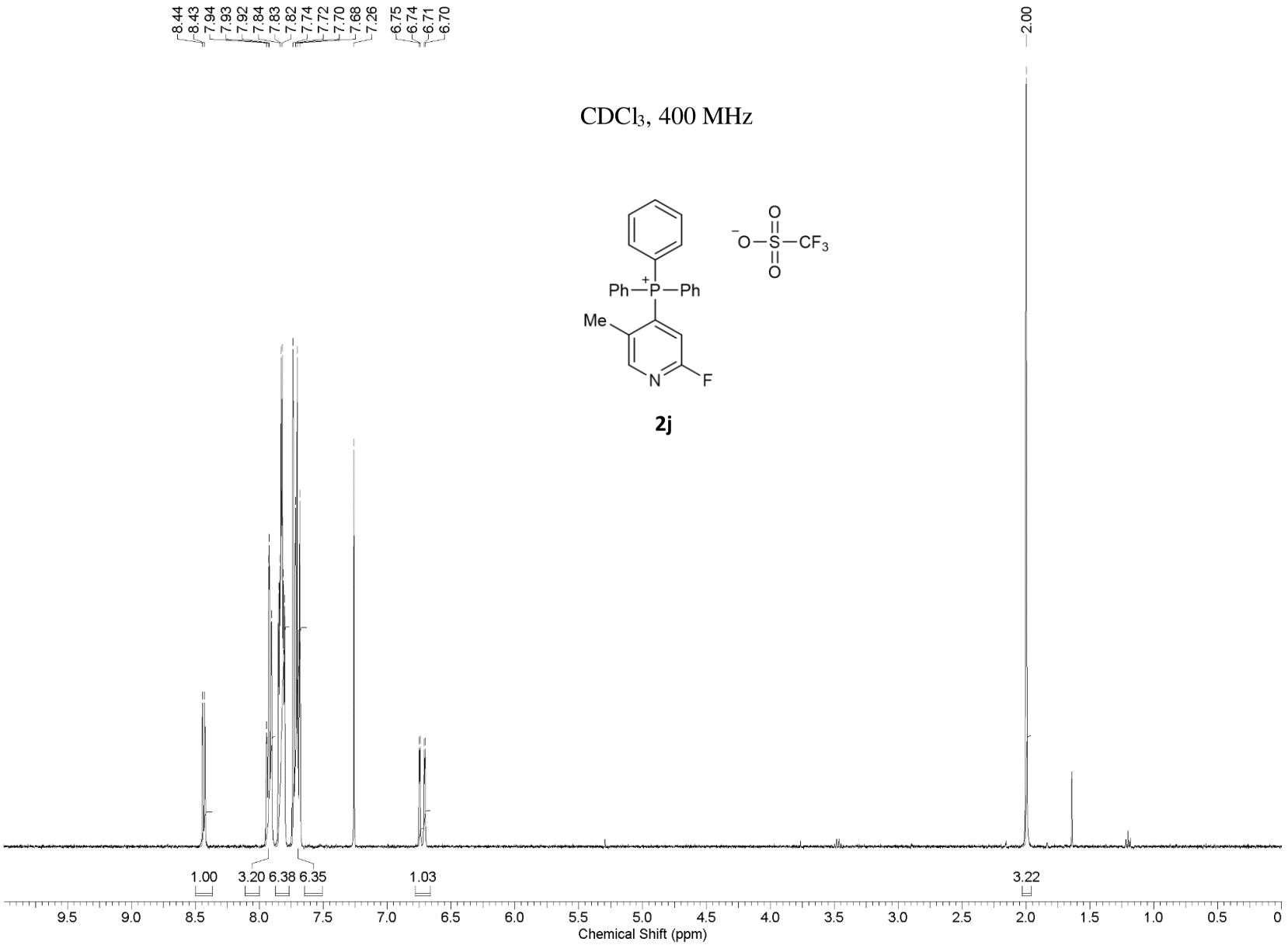

160.55
160.47
148.52
148.40
135.78
135.70
135.51
134.37
134.26
130.82
130.69
126.49
126.39
126.18
125.36
122.26
119.06
117.03
116.16
40.13
39.93
39.71
39.51
39.30
39.08
38.88
32.28
29.95
29.89
21.29
20.80
DMSO-d6, 100 MHz
2g
Chemical Shift (ppm)

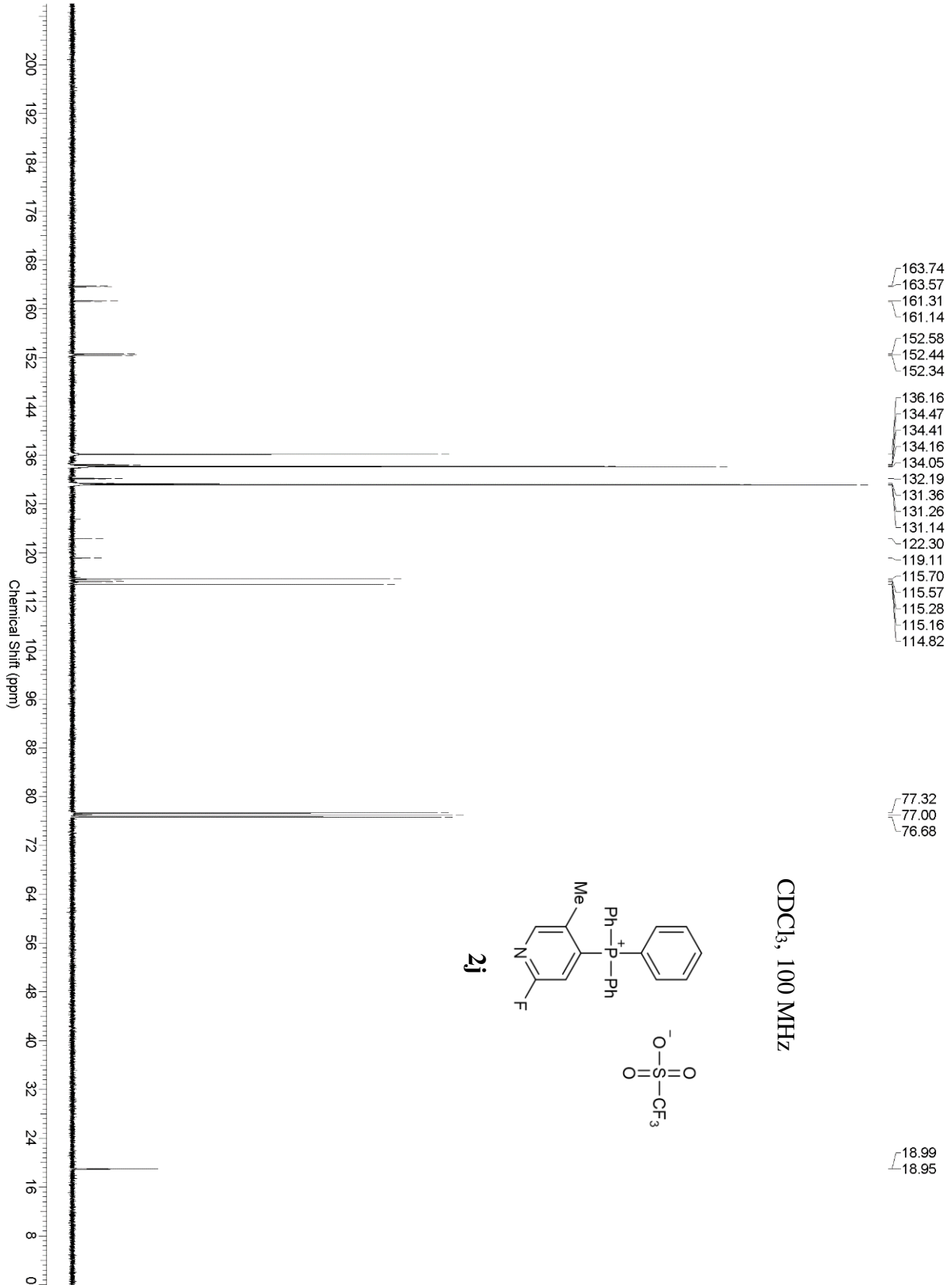

8.84
8.82
8.81
7.82
7.81
7.72
7.71
7.70
7.68
7.60
7.58
7.57
7.55
7.26
6.85
6.84
6.84
6.58
6.58
6.58
6.20
6.20
6.19
2.31
CDCl3, 400 MHz
Ph—P—Ph
O—S—CF3
S
N
Me
2h
1.00
3.11
6.26
6.21
1.72
1.00
0.99
1.01
3.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


162.00
149.50
149.38
135.19
133.84
133.75
130.56
130.43
128.11
128.05
126.48
125.97
125.91
125.81
122.29
117.61
116.72
77.32
77.20
77.00
76.68
23.56
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
CDCl3, 100 MHz
2h
Ph
P
Ph
N
Me
S
O
S
O
O
CF3


8.97
8.95
7.86
7.86
7.76
7.75
7.74
7.73
7.72
7.71
7.69
7.26
7.19
7.17
7.11
7.07
6.67
6.65
6.65
2.66
CDCl3, 400 MHz
Ph—P—Ph
O—S—CF3
N
Me
2i
0.94
2.88
12.00
1.79
1.93
0.94
1.88
2.88
Chemical Shift (ppm)

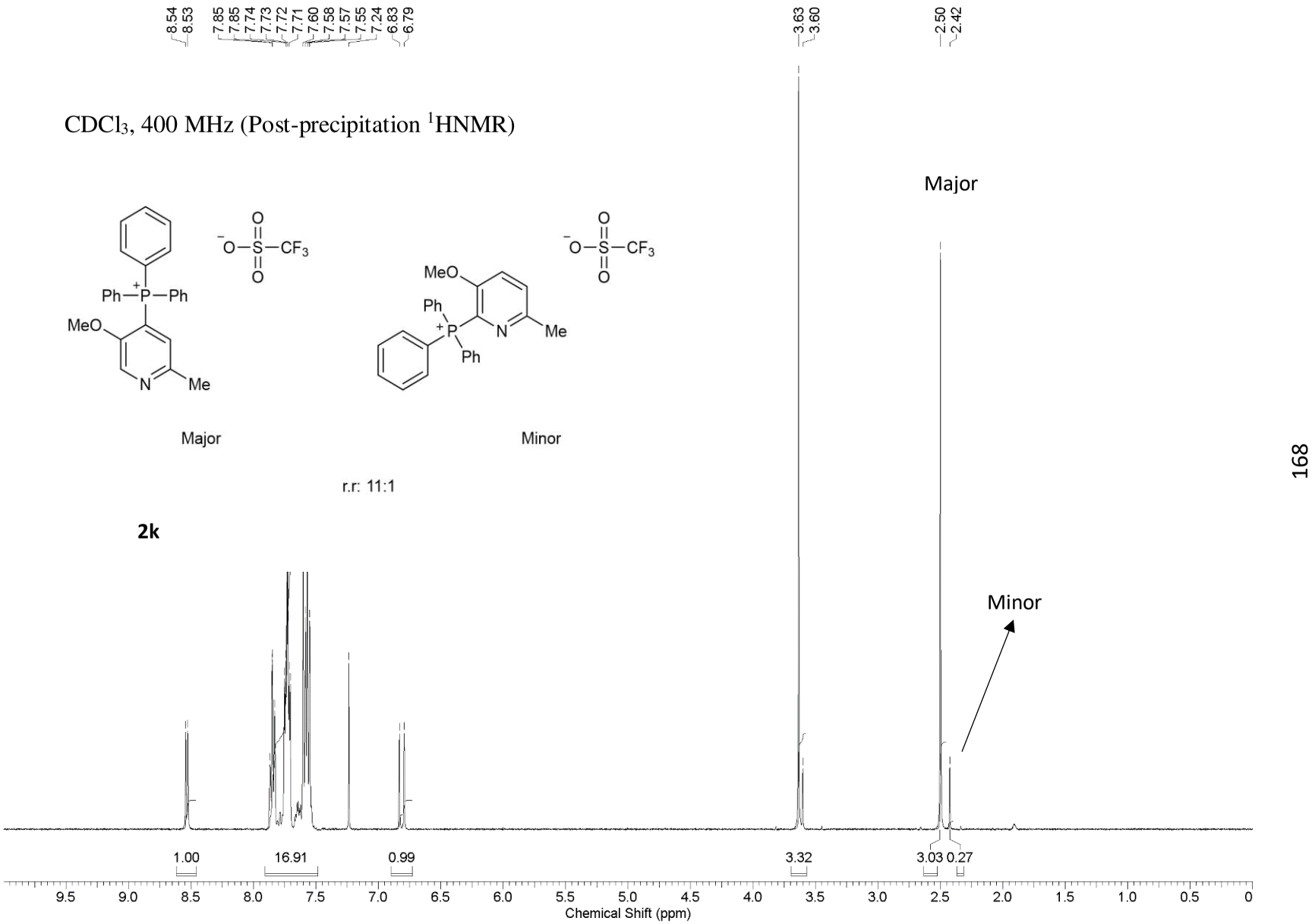

160.45
160.34
154.07
154.01
135.73
134.26
134.16
130.83
130.73
130.60
129.87
128.32
128.22
128.06
122.35
120.39
119.90
116.27
115.37
103.30
84.00
83.93
77.32
77.00
76.68
24.83
CDCl3, 100 MHz
2i
Chemical Shift (ppm)

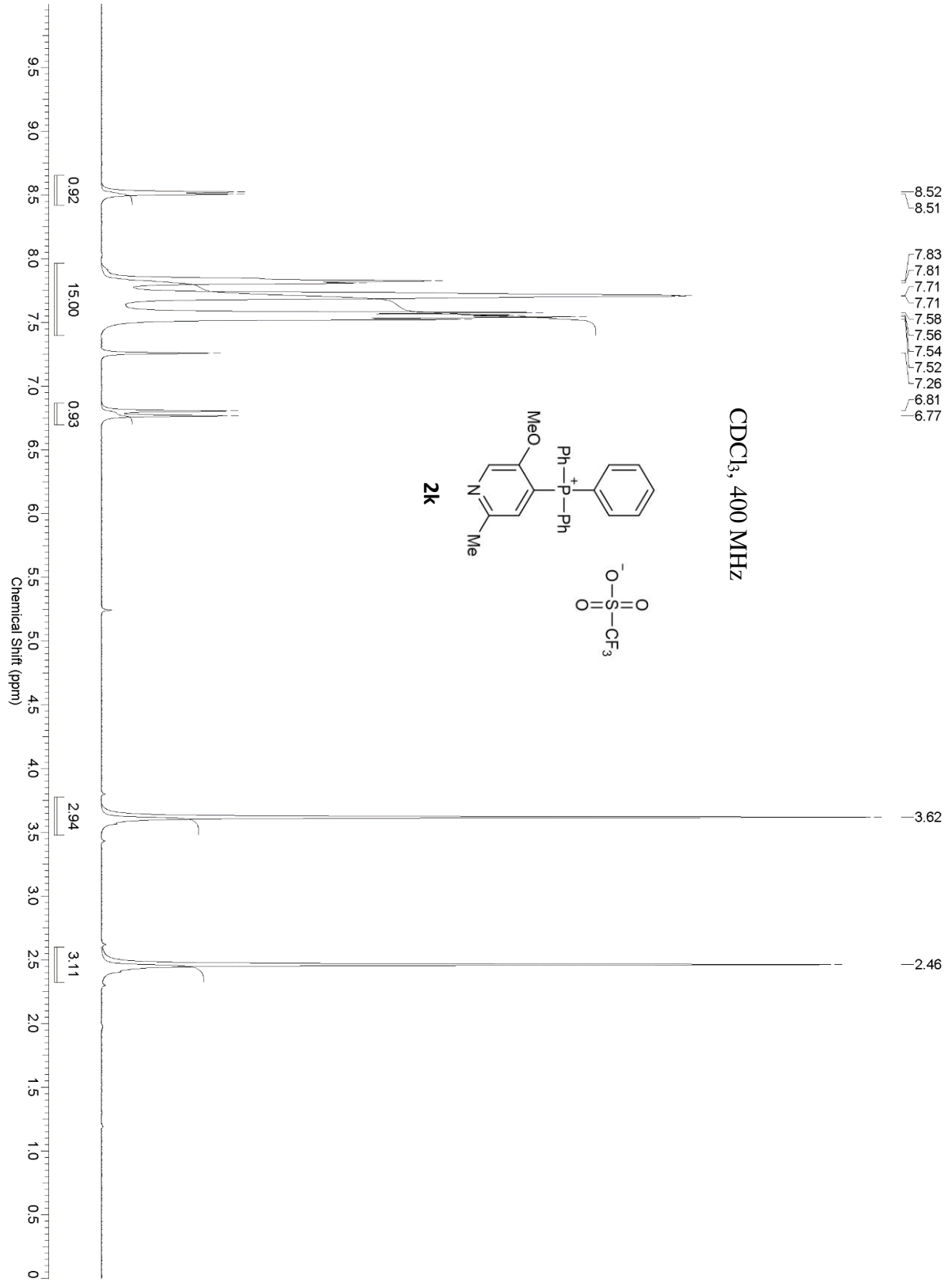

8.44
8.43
7.94
7.93
7.92
7.84
7.83
7.82
7.74
7.72
7.70
7.68
7.26
6.75
6.74
6.71
6.70
2.00
CDCl3, 400 MHz
Ph—P—Ph
Me
N
F
O
O—S—CF3
O
2j
1.00
3.20
6.38
6.35
1.03
3.22
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

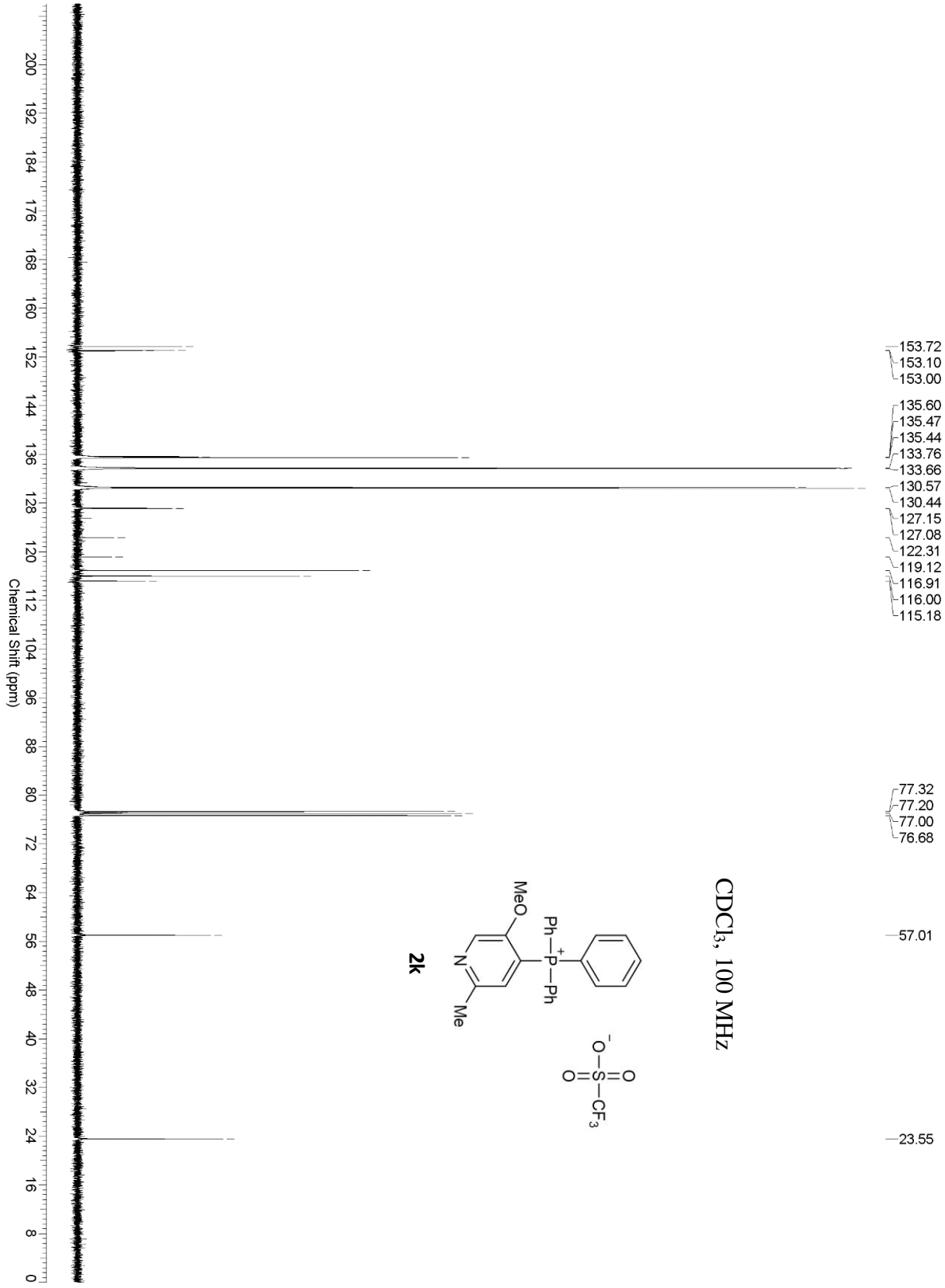


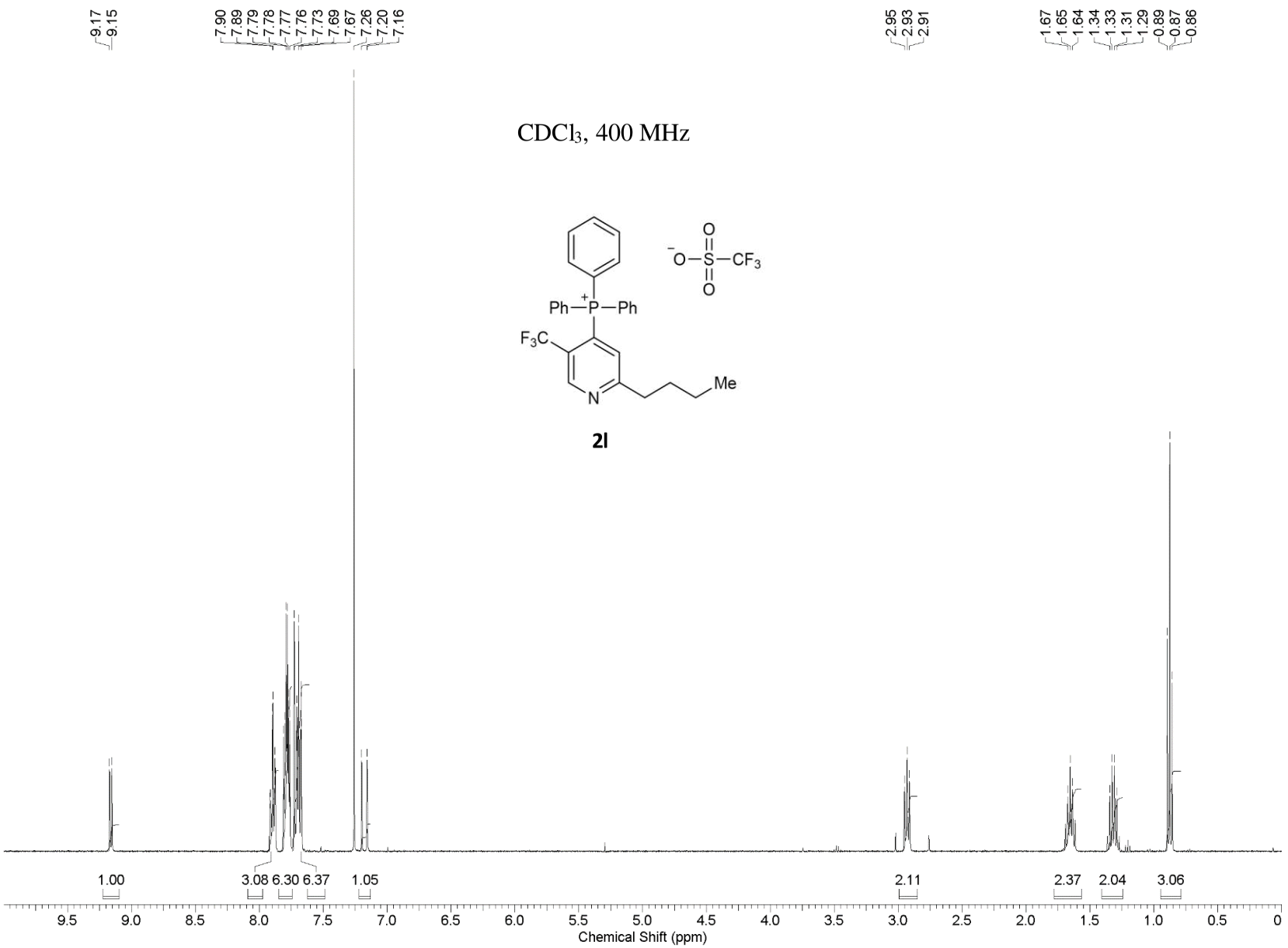
2j

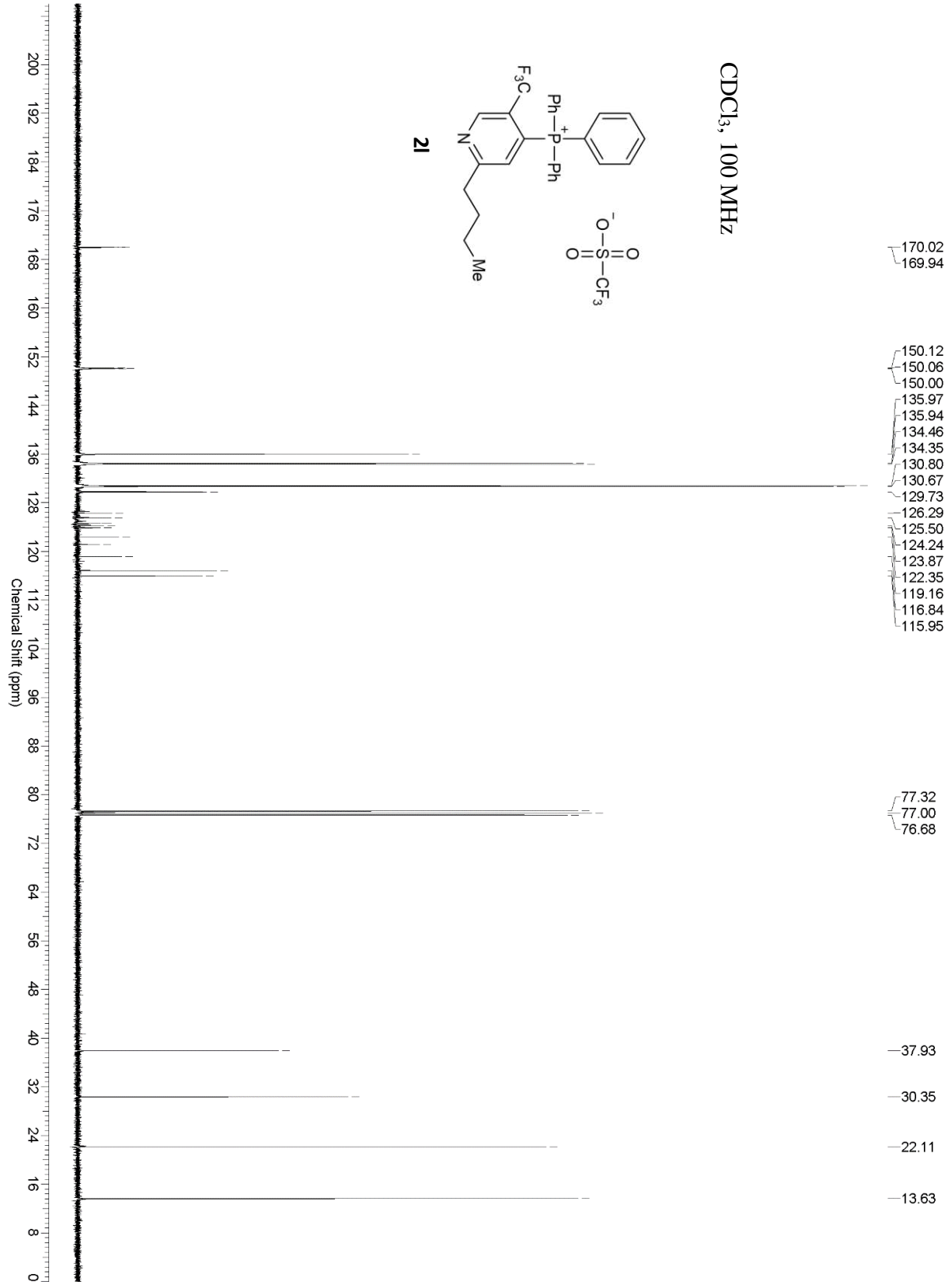
$CDCl_3$, 100 MHz

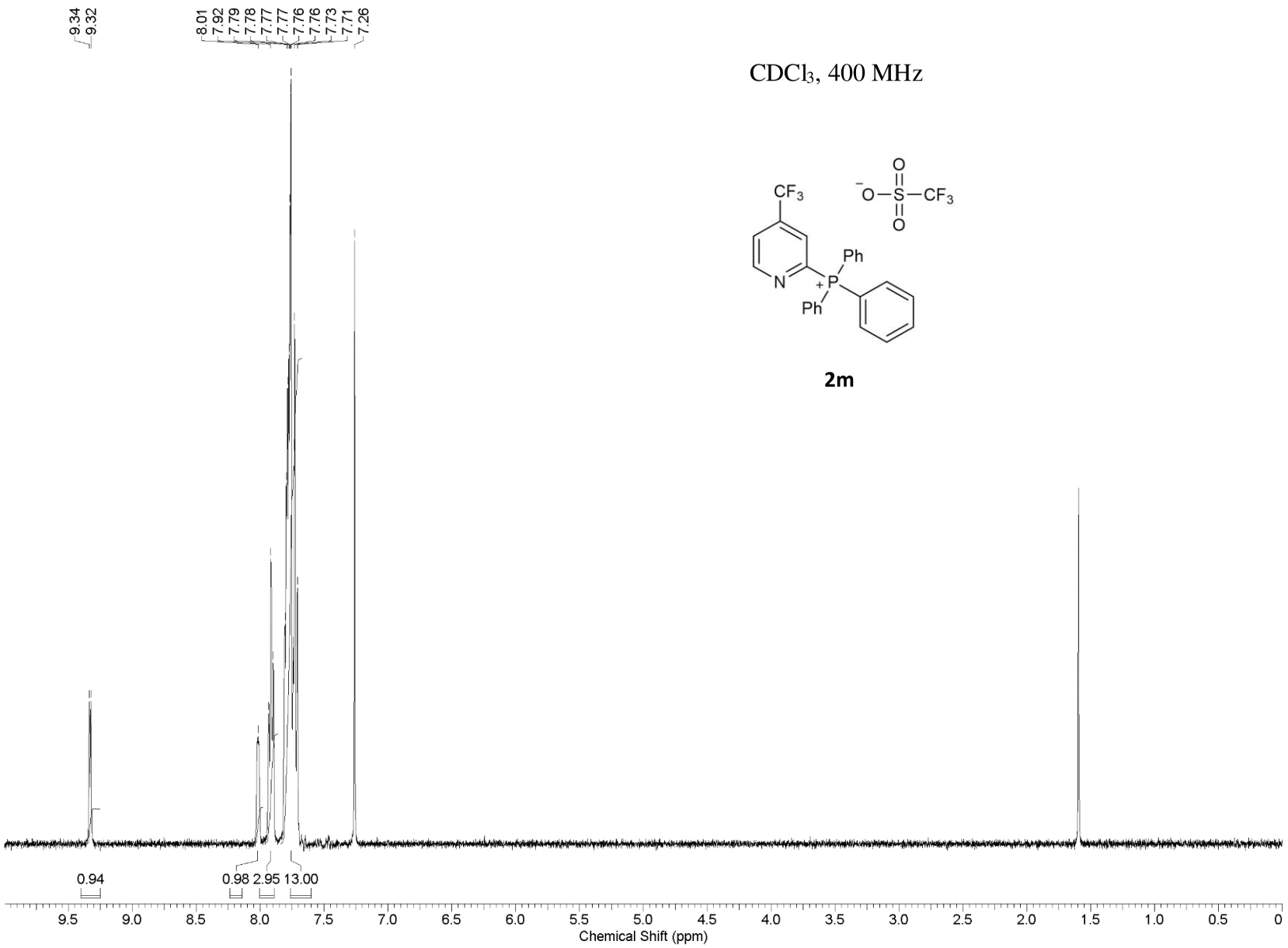

8.54
8.53
7.85
7.85
7.74
7.73
7.72
7.71
7.60
7.58
7.57
7.55
7.24
6.83
6.79
3.63
3.60
2.50
2.42
CDCl3, 400 MHz (Post-precipitation 1HNMR)
Major
Minor
r.r: 11:1
2k
Major
Minor
1.00
16.91
0.99
3.32
3.03
0.27
Chemical Shift (ppm)

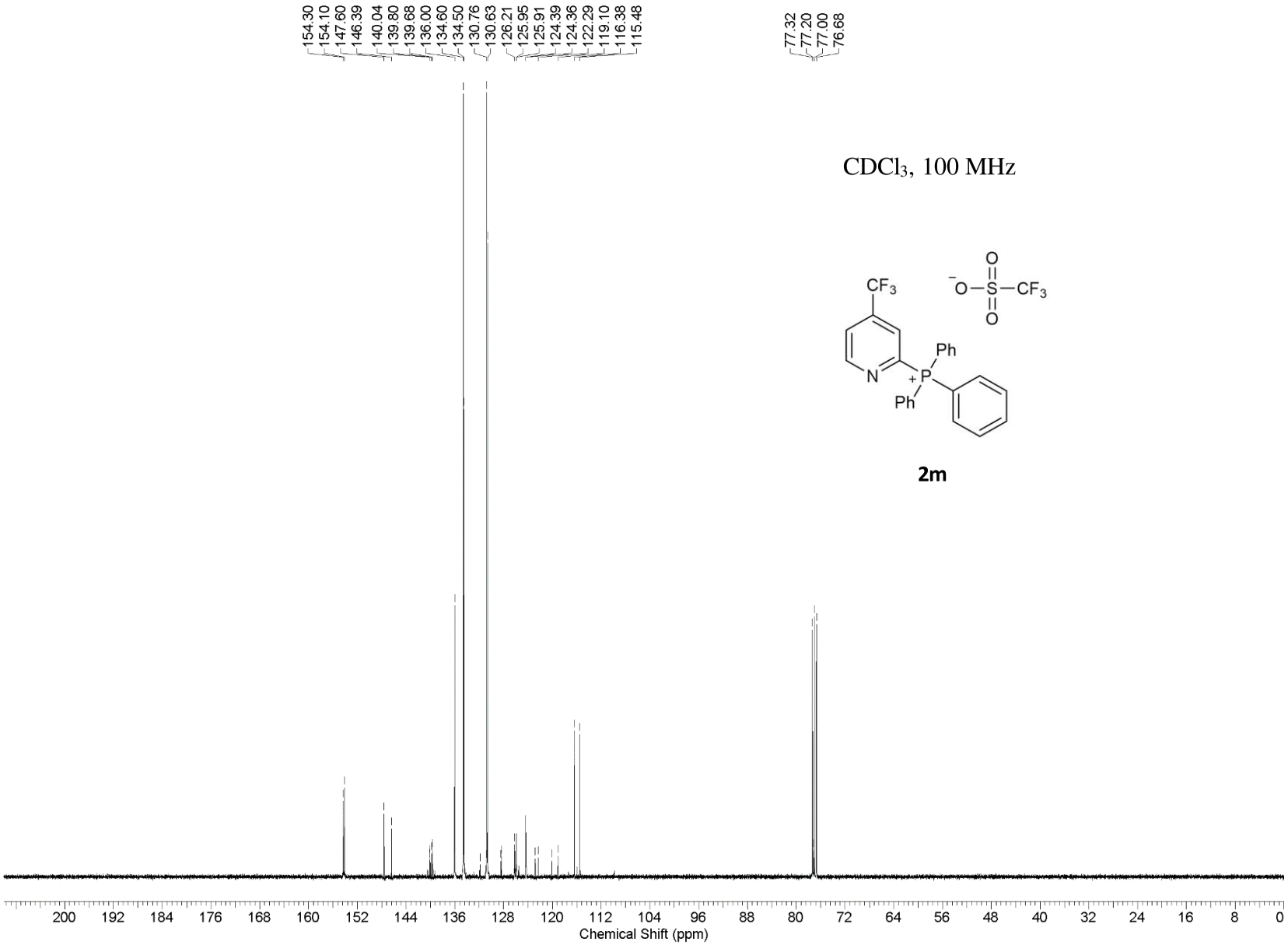

CDCl3, 400 MHz
2k
MeO
Ph—P—Ph
N
Me
O
S
CF3
8.52
8.51
7.83
7.81
7.71
7.71
7.58
7.56
7.54
7.52
7.26
6.81
6.77
3.62
2.46
0.92
15.00
0.93
2.94
3.11
Chemical Shift (ppm)


153.72
153.10
153.00
135.60
135.47
135.44
133.76
133.66
130.57
130.44
127.15
127.08
122.31
119.12
116.91
116.00
115.18
77.32
77.20
77.00
76.68
57.01
23.55
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
CDCl3, 100 MHz
2k
MeO
Ph
P
Ph
N
Me
O
S
O
O
CF3


9.17
9.15
7.90
7.89
7.79
7.78
7.77
7.76
7.73
7.69
7.67
7.26
7.20
7.16
2.95
2.93
2.91
1.67
1.65
1.64
1.34
1.33
1.31
1.29
0.89
0.87
0.86
CDCl3, 400 MHz
Ph
P
Ph
F3C
N
Me
O
S
CF3
2l
1.00
3.08
6.30
6.37
1.05
2.11
2.37
2.04
3.06
Chemical Shift (ppm)

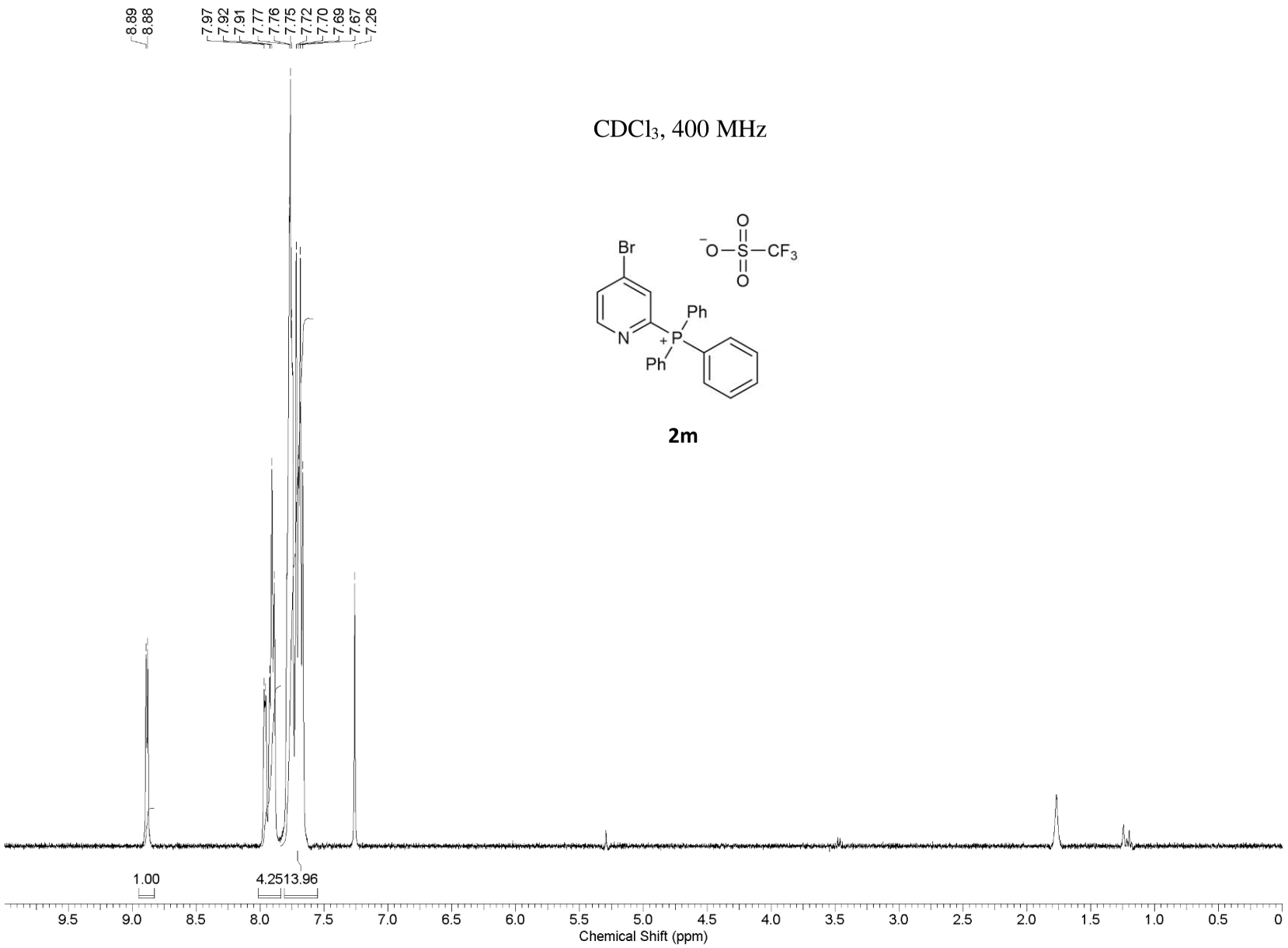

CDCl3, 100 MHz
2l
Chemical Shift (ppm)
170.02
169.94
150.12
150.06
150.00
135.97
135.94
134.46
134.35
130.80
130.67
129.73
126.29
125.50
124.24
123.87
122.35
119.16
116.84
115.95
77.32
77.00
76.68
37.93
30.35
22.11
13.63


9.34
9.32
8.01
7.92
7.79
7.78
7.77
7.77
7.76
7.76
7.73
7.71
7.26
CDCl3, 400 MHz
CF3
O
O−S−CF3
O
Ph
N
P
Ph
2m
0.94
0.98
2.95
13.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)



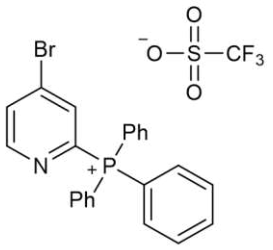
$CDCl_3$, 100 MHz

2m

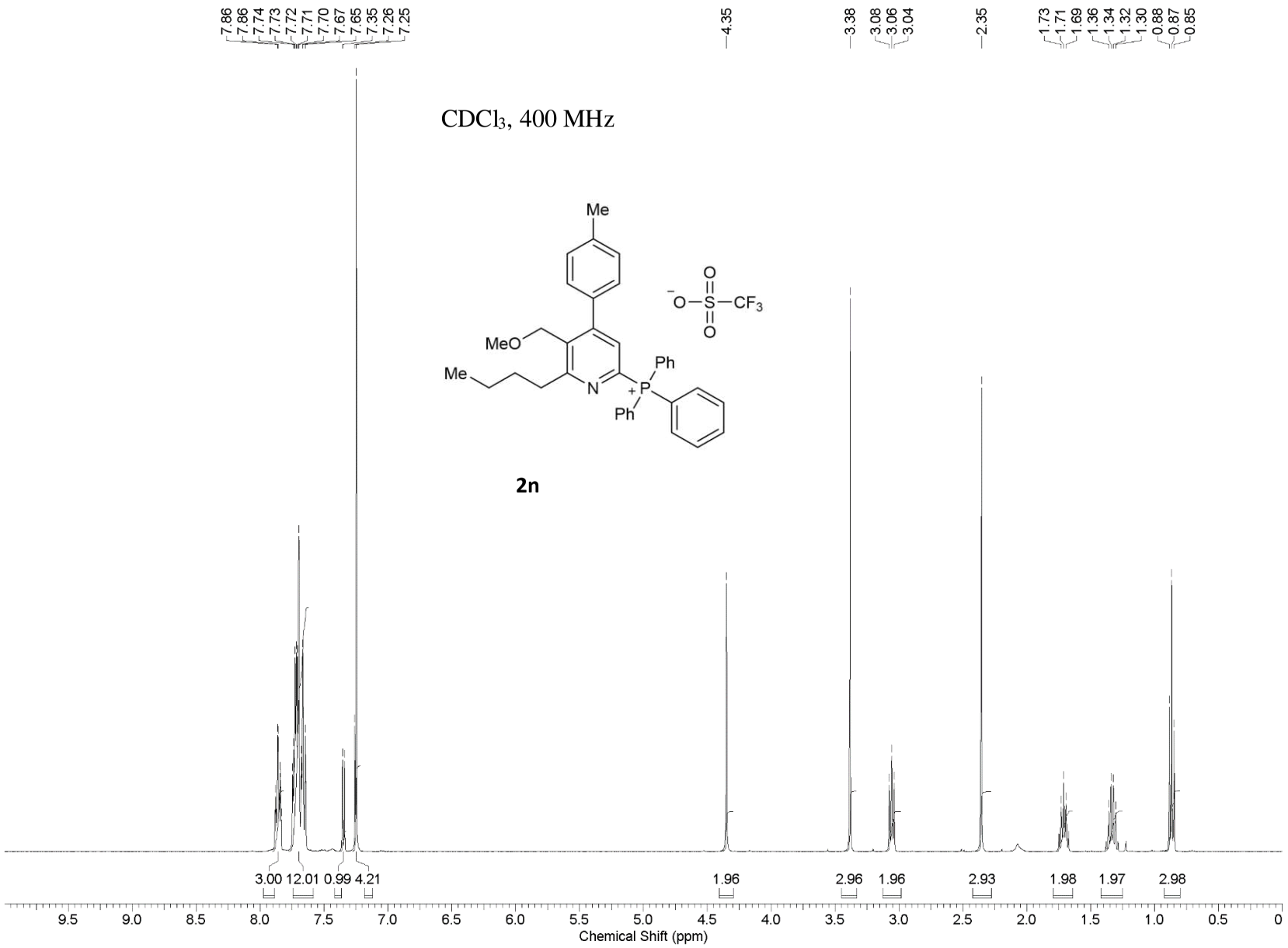

8.89
8.88
7.97
7.92
7.91
7.77
7.76
7.75
7.72
7.70
7.69
7.67
7.26
CDCl3, 400 MHz
Br
O
O
O
CF3
Ph
N
P
Ph
1.00
4.25
13.96
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

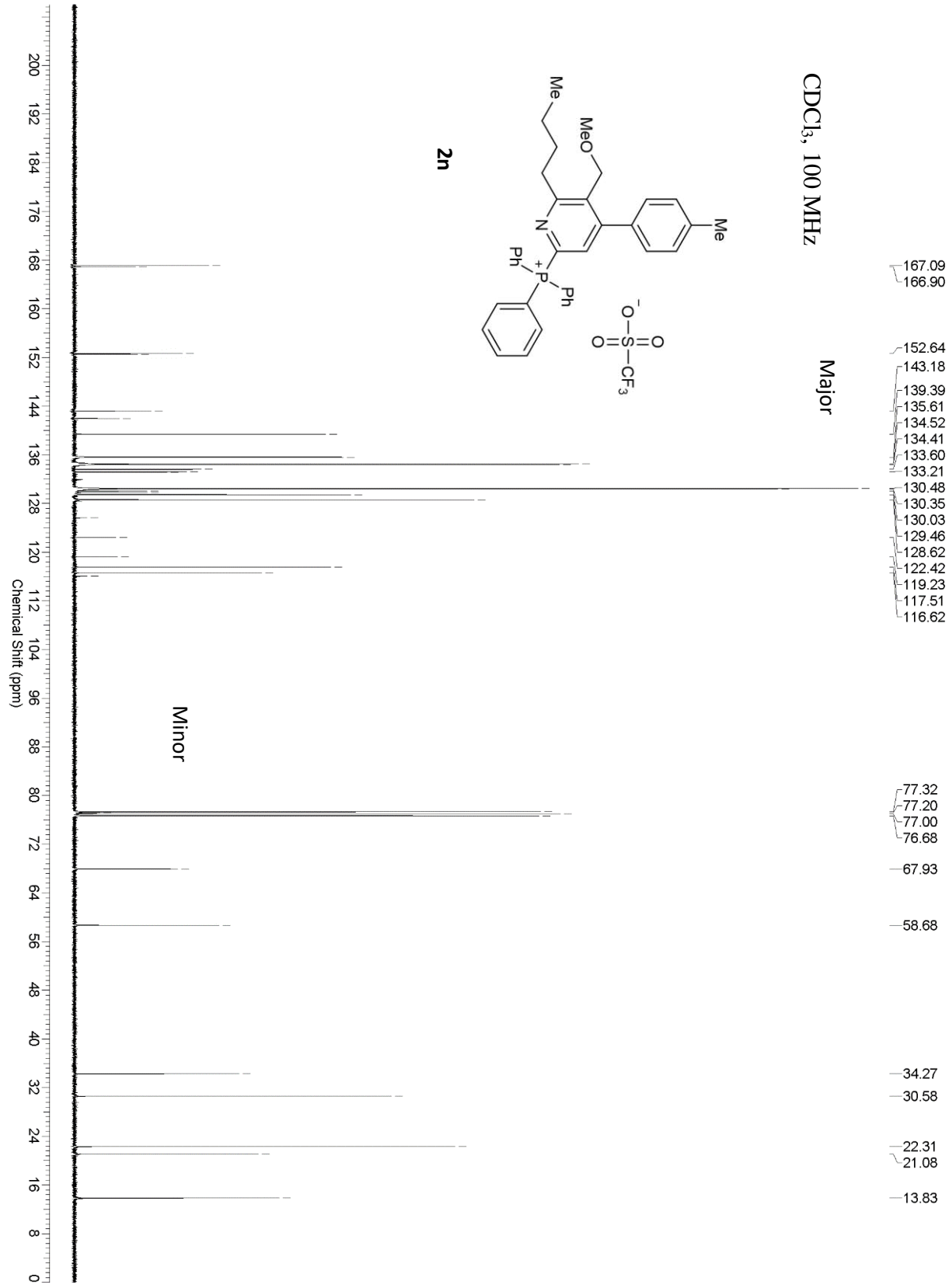
2m

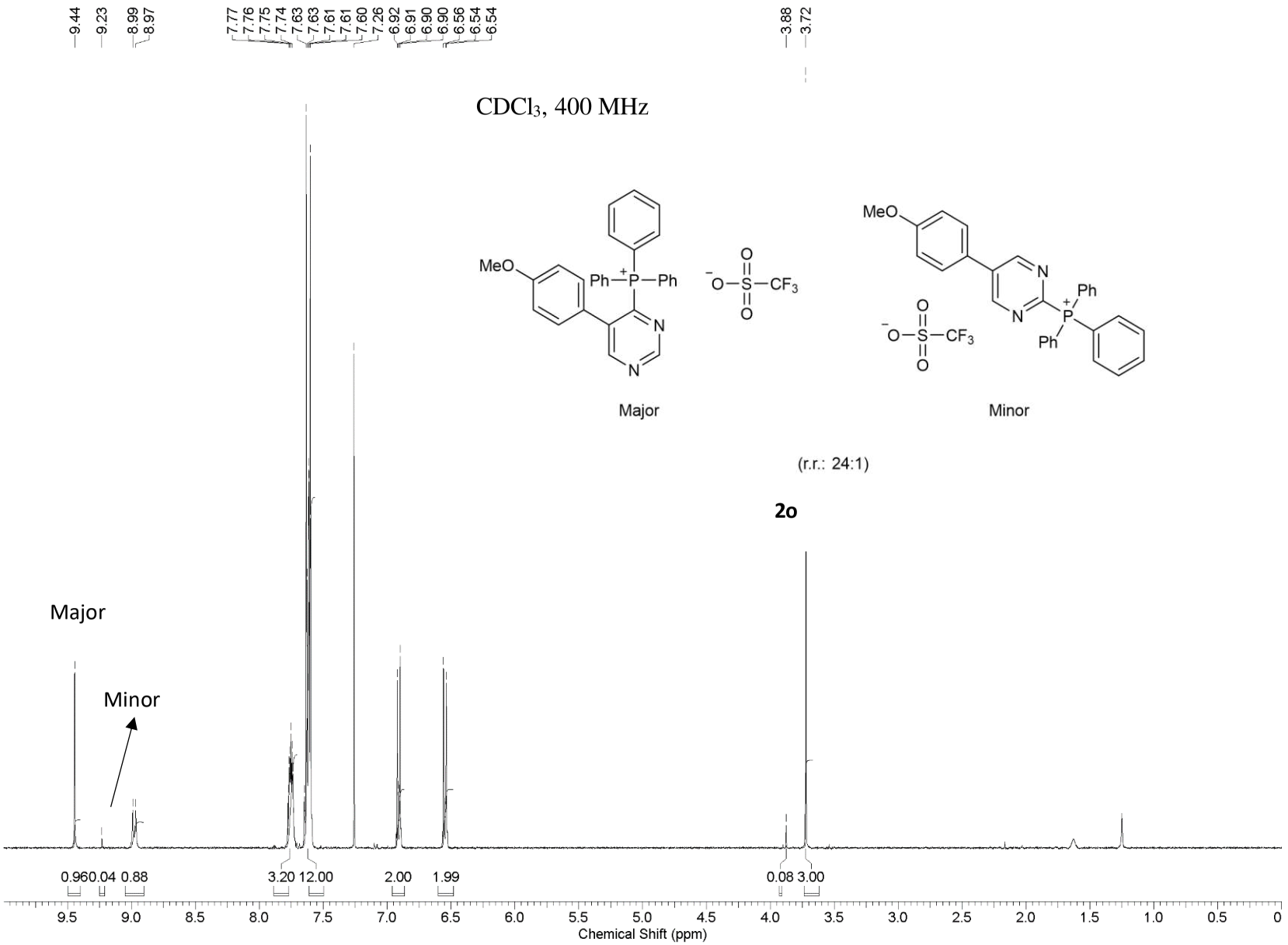
$CDCl_3$, 100 MHz

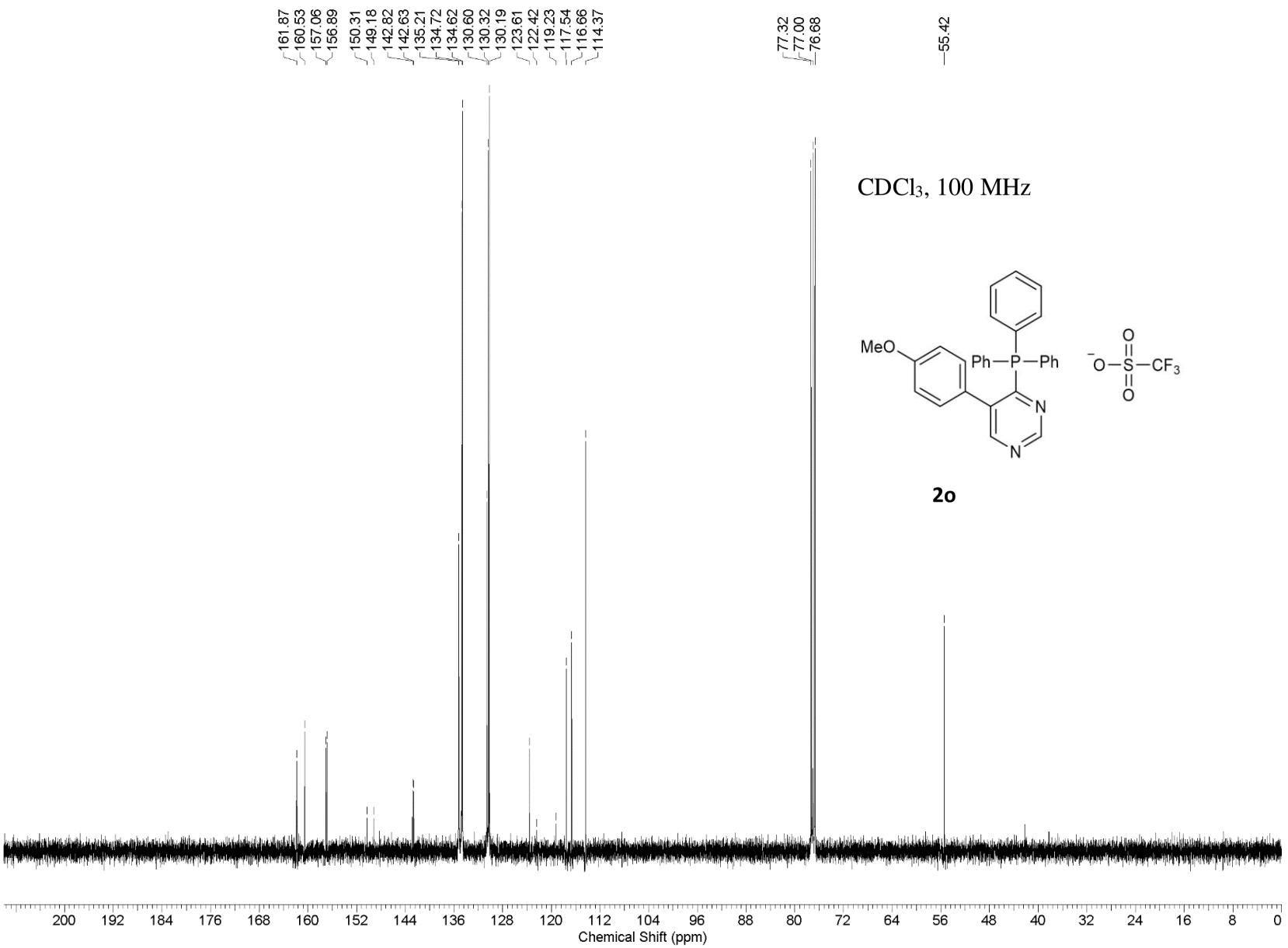


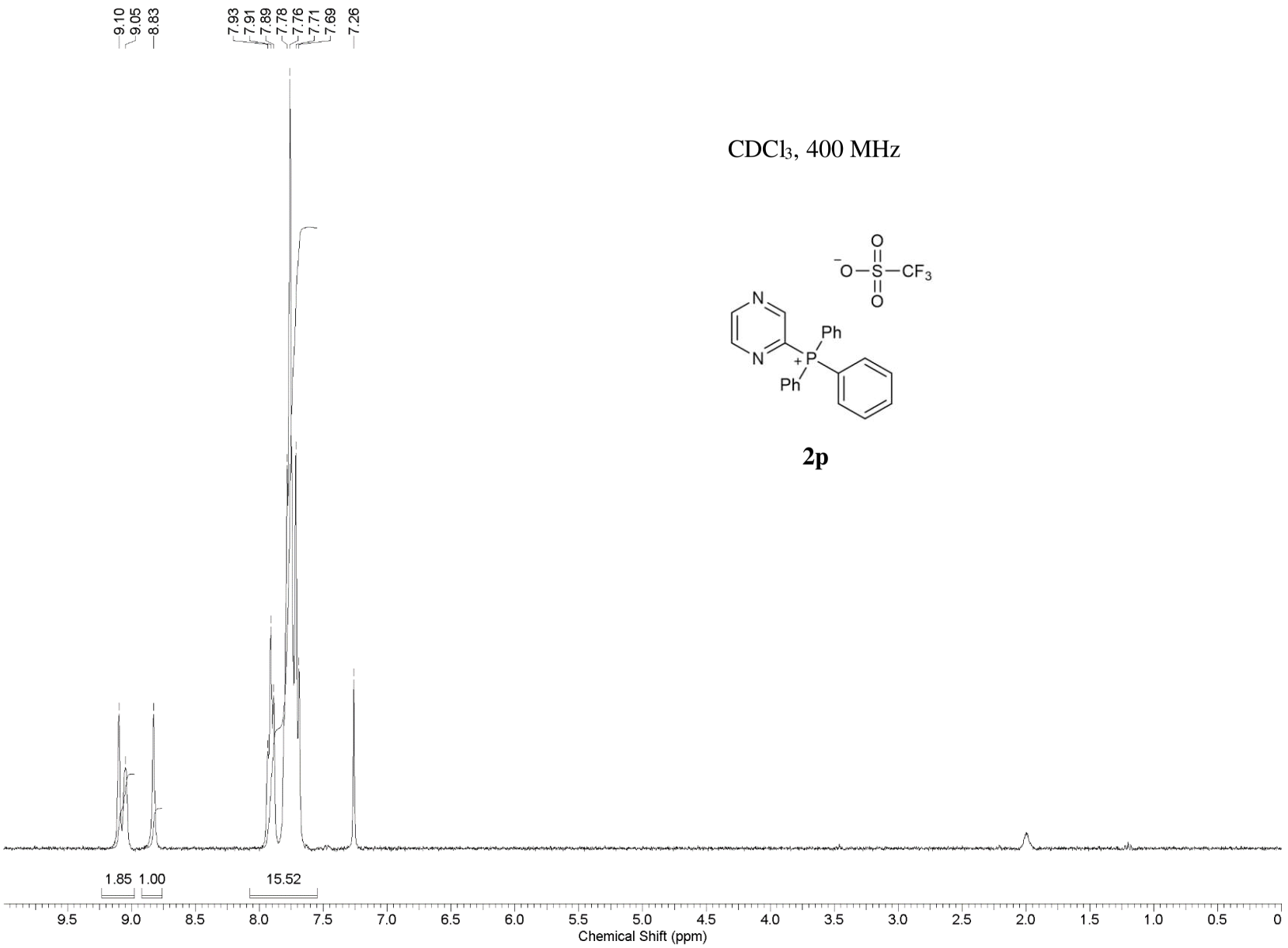
2m


7.86
7.86
7.74
7.73
7.72
7.71
7.70
7.67
7.65
7.35
7.26
7.25
4.35
3.38
3.08
3.06
3.04
2.35
1.73
1.71
1.69
1.36
1.34
1.32
1.30
0.88
0.87
0.85
CDCl3, 400 MHz
Me
MeO
Me
N
P
Ph
Ph
O
O
O
O
S
CF3
2n
3.00 12.01 0.99 4.21
1.96
2.96 1.96
2.93
1.98 1.97
2.98
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


CDCl3, 100 MHz
2n
Major
Minor
Me
MeO
Me
N
Ph
P
Ph
Ph
O
S
O
O
CF3
167.09
166.90
152.64
143.18
139.39
135.61
134.52
134.41
133.60
133.21
130.48
130.35
130.03
129.46
128.62
122.42
119.23
117.51
116.62
77.32
77.20
77.00
76.68
67.93
58.68
34.27
30.58
22.31
21.08
13.83
Chemical Shift (ppm)

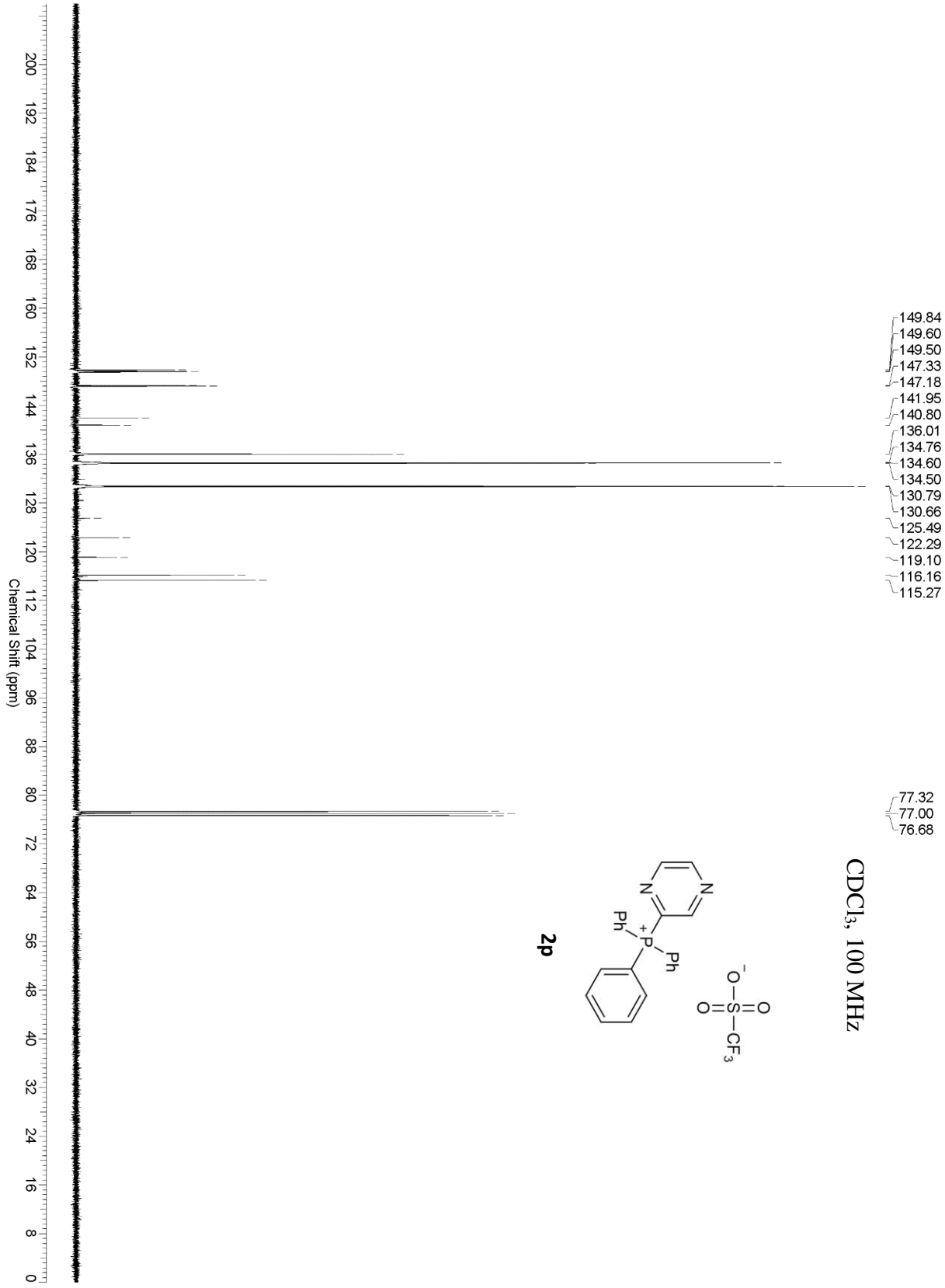

9.44
9.23
8.99
8.97
7.77
7.76
7.75
7.74
7.63
7.63
7.61
7.61
7.60
7.26
6.92
6.91
6.90
6.90
6.56
6.54
6.54
3.88
3.72
CDCl3, 400 MHz
MeO
Ph
P
Ph
N
N
O
O
S
O
CF3
Major
MeO
N
N
Ph
P
Ph
O
O
S
O
CF3
Minor
(r.r.: 24:1)
2o
Major
Minor
0.96
0.04
0.88
3.20
12.00
2.00
1.99
0.08
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

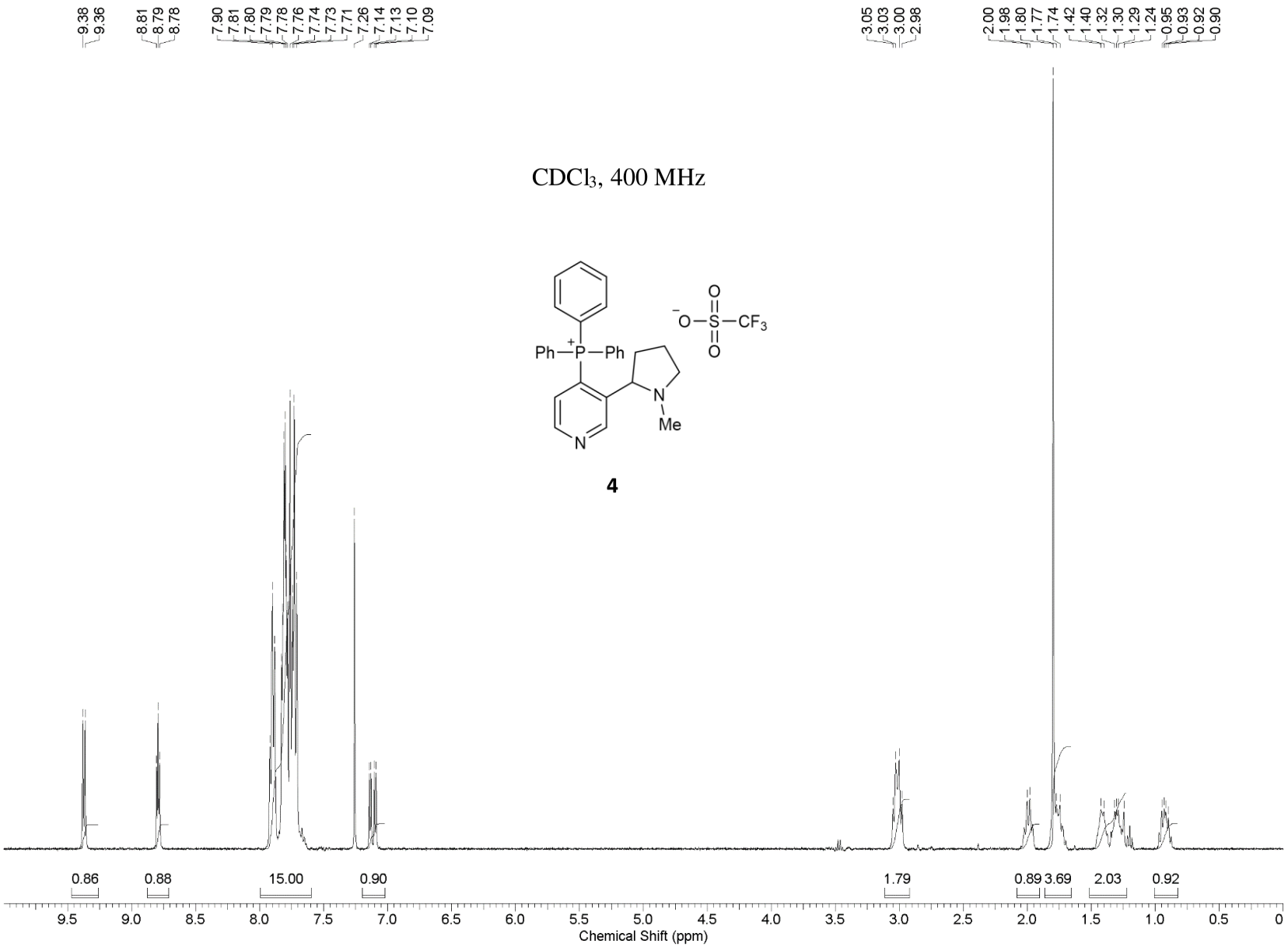

161.87
160.53
157.06
156.89
150.31
149.18
142.82
142.63
135.21
134.72
134.62
130.60
130.32
130.19
123.61
122.42
119.23
117.54
116.66
114.37
77.32
77.00
76.68
55.42
CDCl3, 100 MHz
MeO
Ph—P—Ph
N
N
O
O—S—CF3
O
O
2o
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

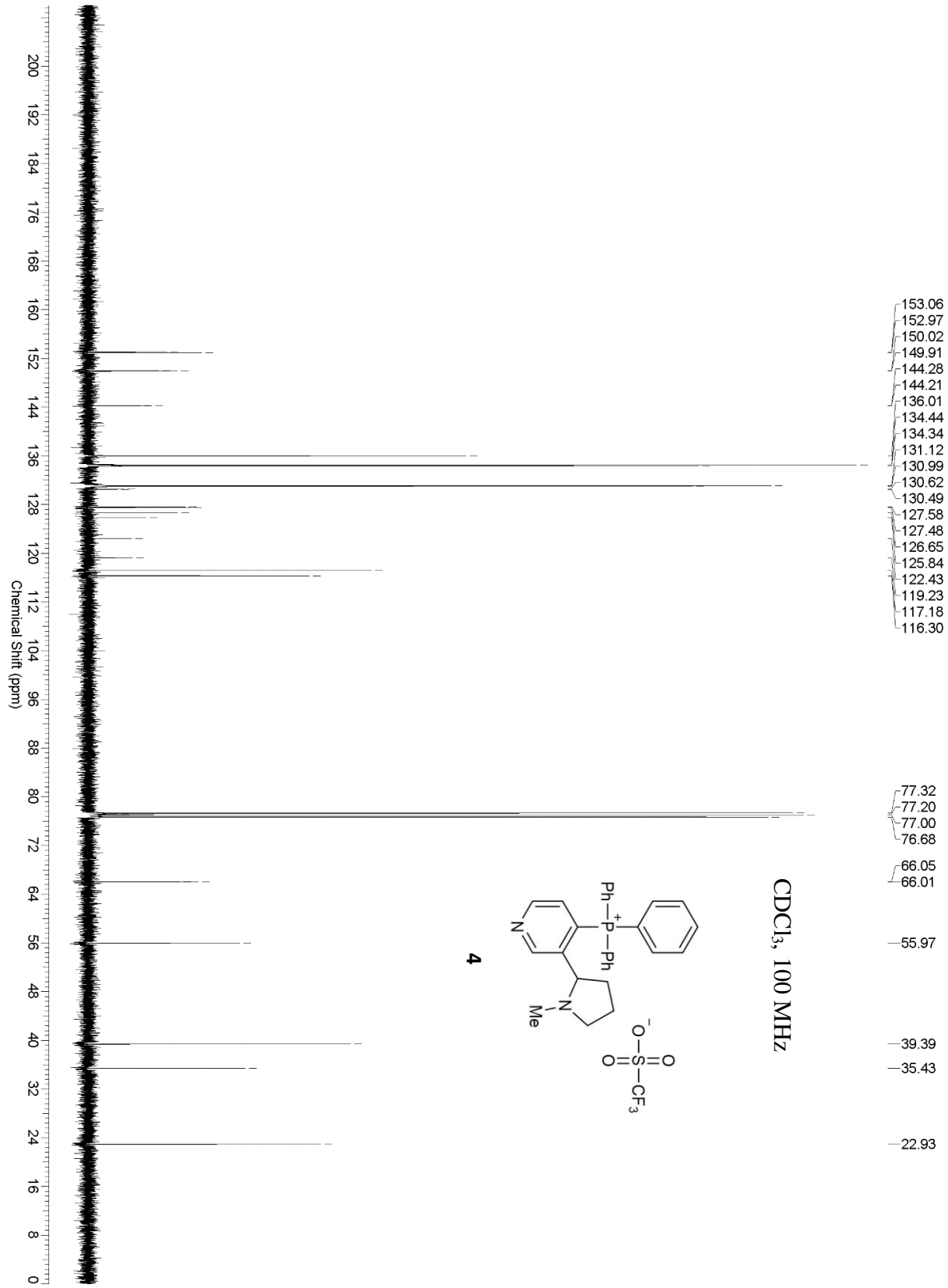


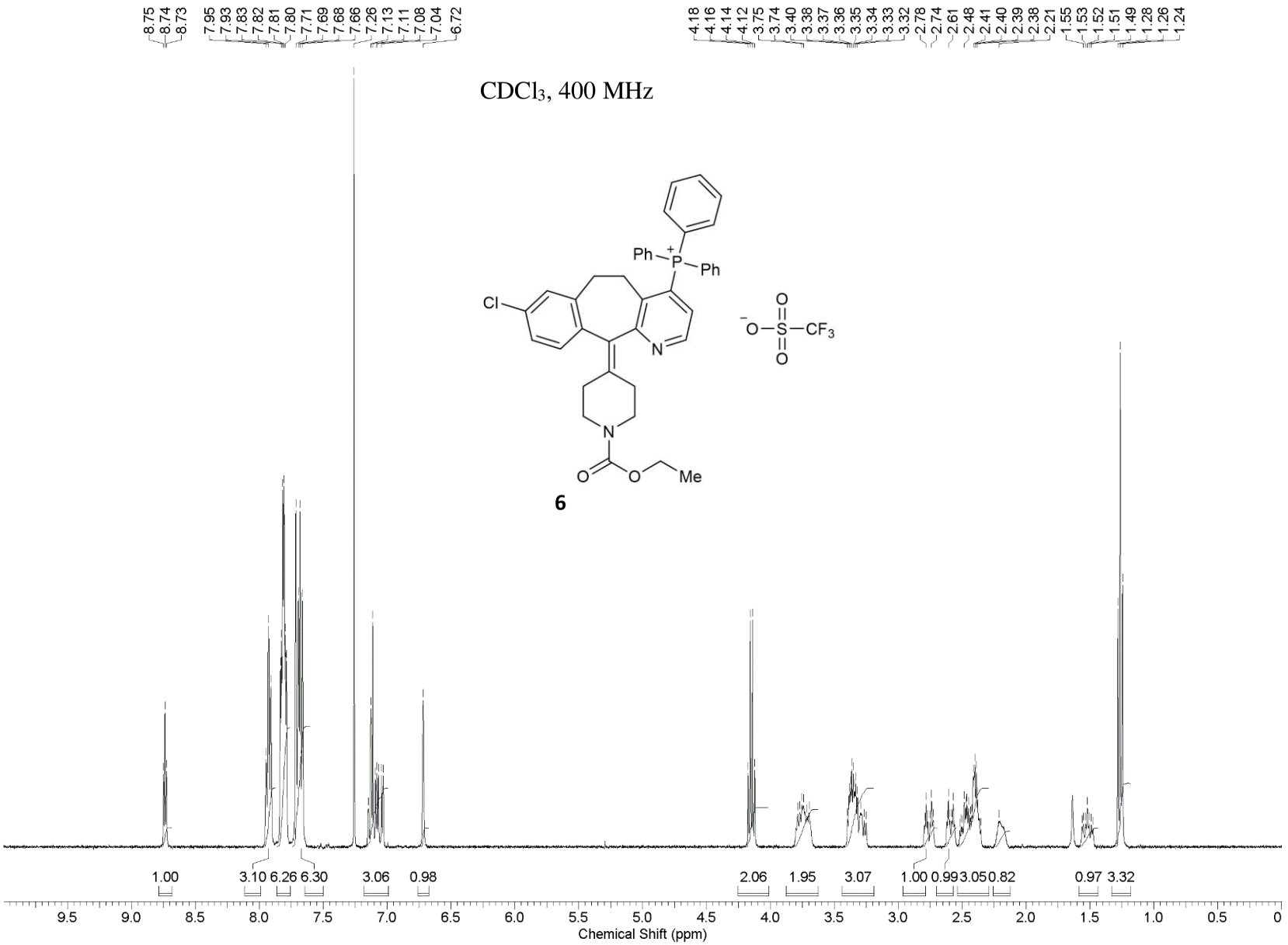
$CDCl_3$, 400 MHz

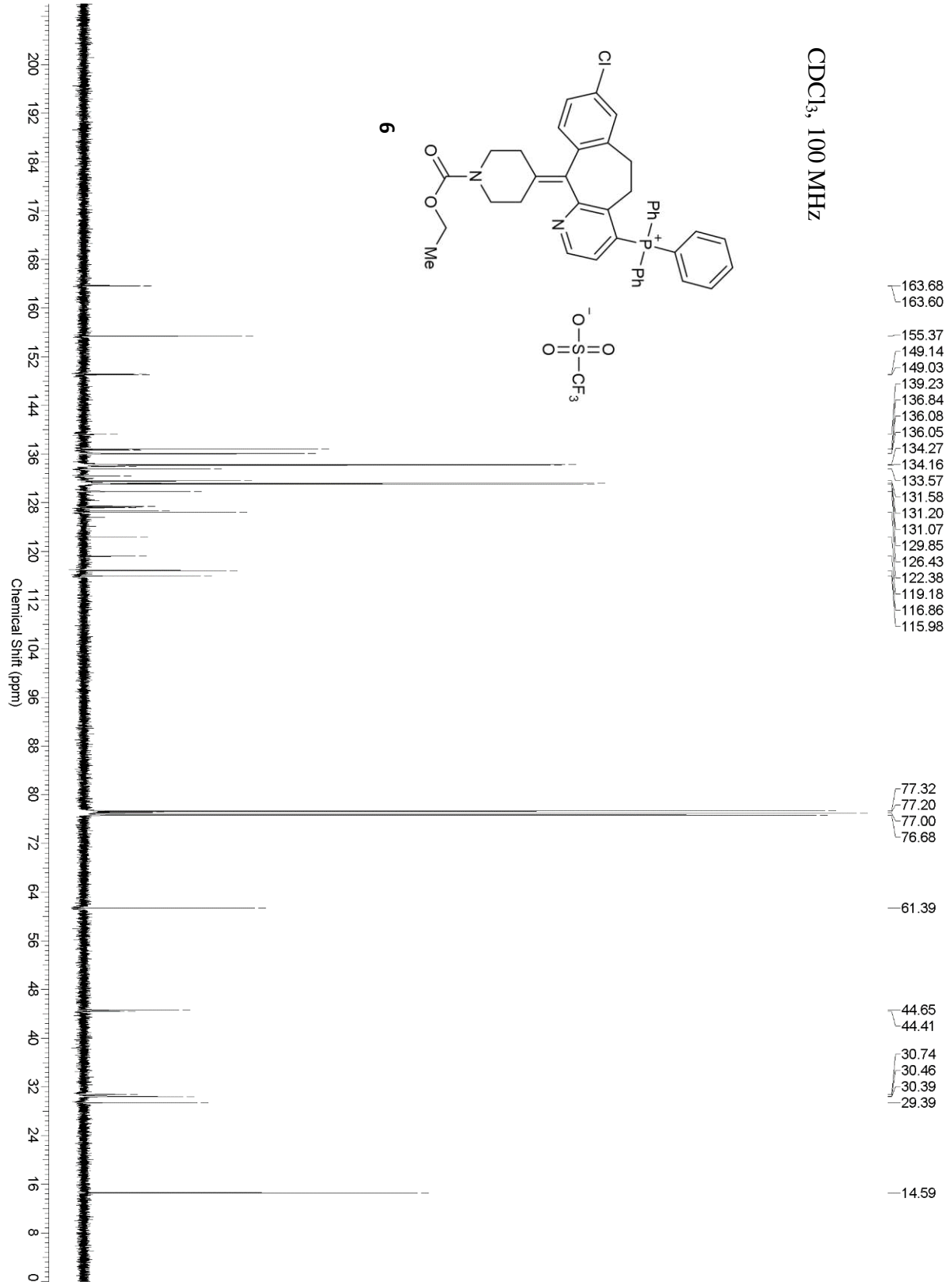
2p

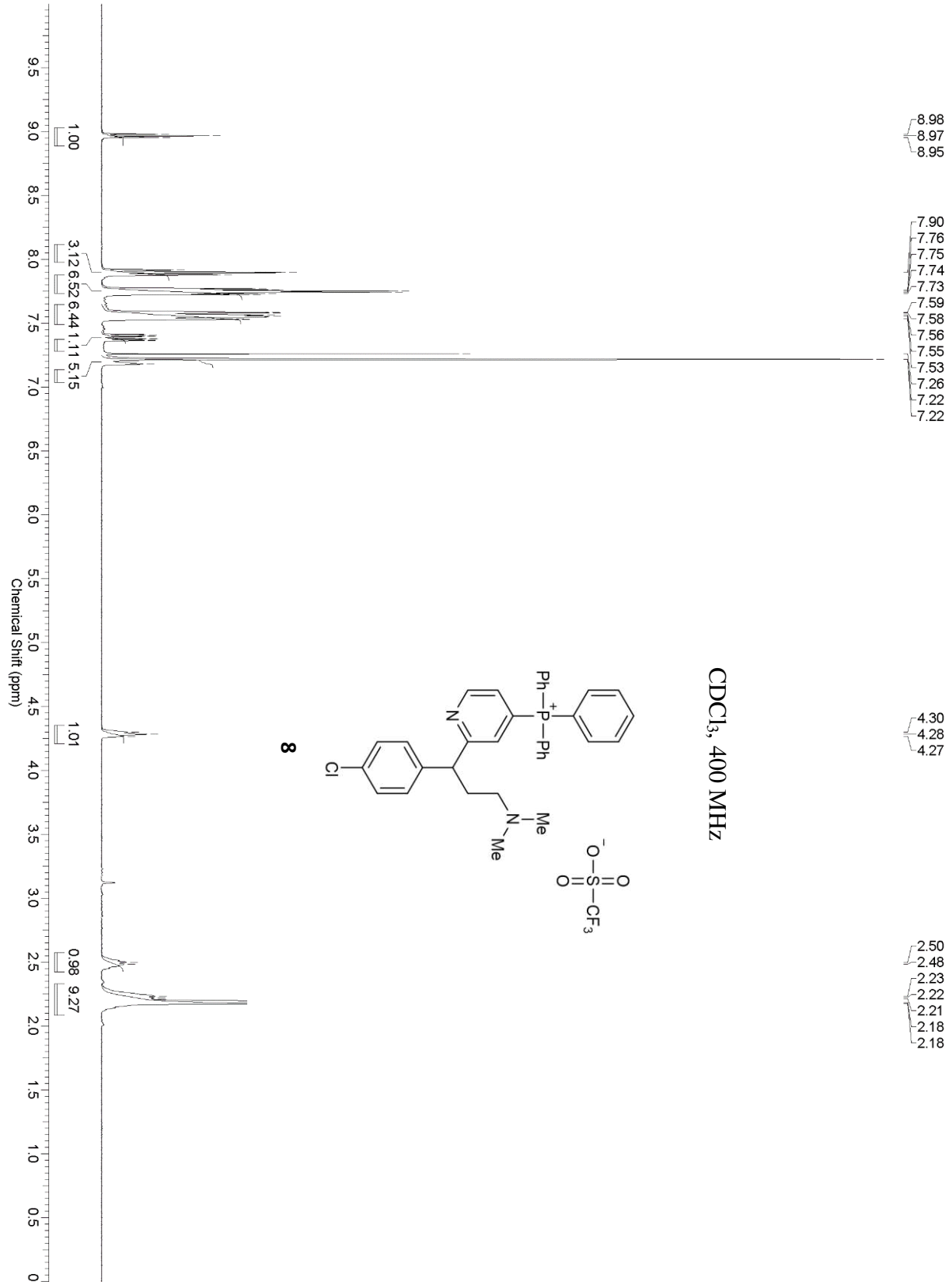

149.84
149.60
149.50
147.33
147.18
141.95
140.80
136.01
134.76
134.60
134.50
130.79
130.66
125.49
122.29
119.10
116.16
115.27
77.32
77.00
76.68
CDCl3, 100 MHz
2p
Chemical Shift (ppm)

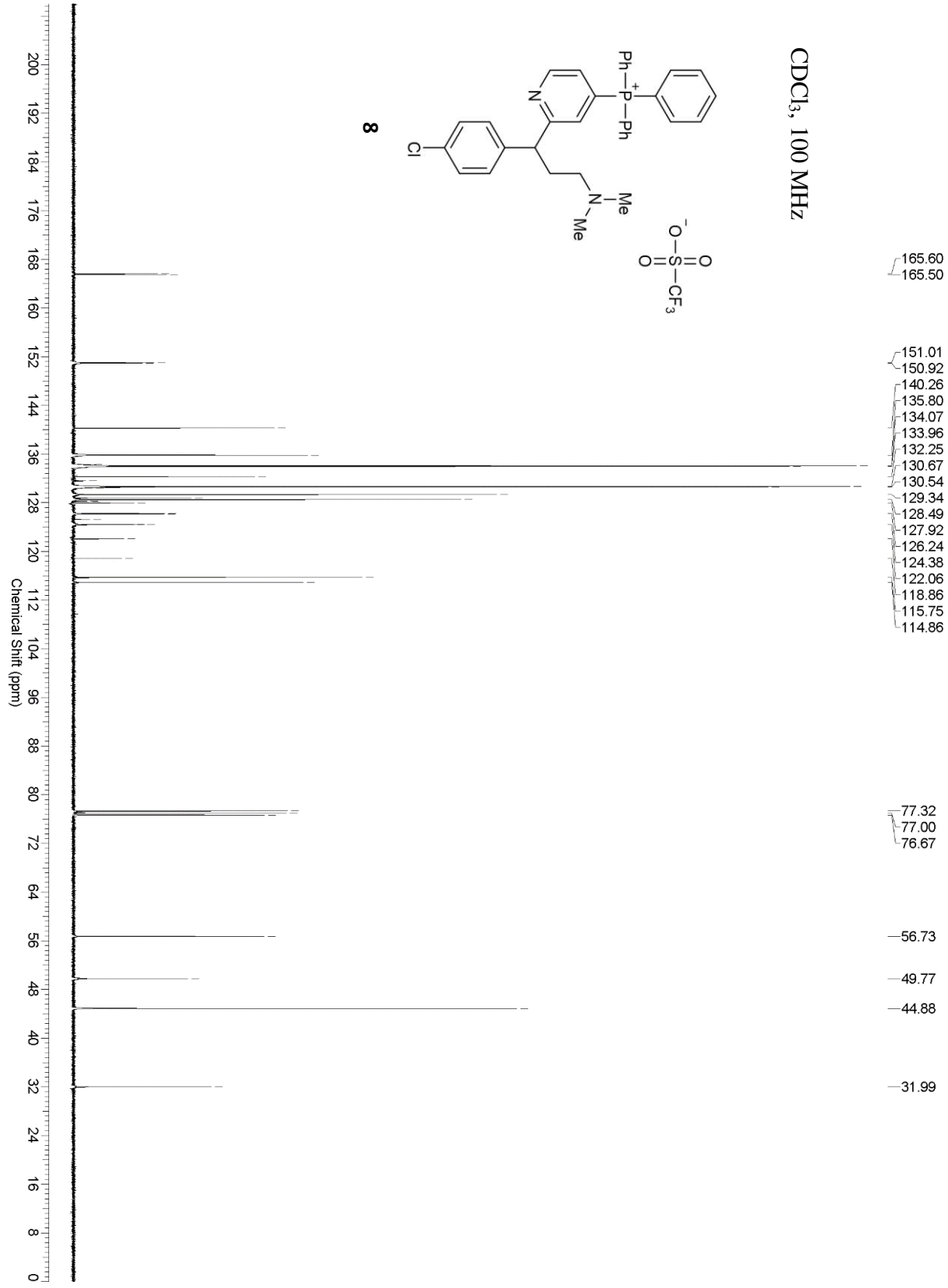

9.38
9.36
8.81
8.79
8.78
7.90
7.81
7.80
7.79
7.78
7.76
7.74
7.73
7.71
7.26
7.14
7.13
7.10
7.09
3.05
3.03
3.00
2.98
2.00
1.98
1.80
1.77
1.74
1.42
1.40
1.32
1.30
1.29
1.24
0.95
0.93
0.92
0.90
CDCl3, 400 MHz
Ph—P—Ph
O—S—CF3
N
Me
4
0.86
0.88
15.00
0.90
1.79
0.89
3.69
2.03
0.92
Chemical Shift (ppm)

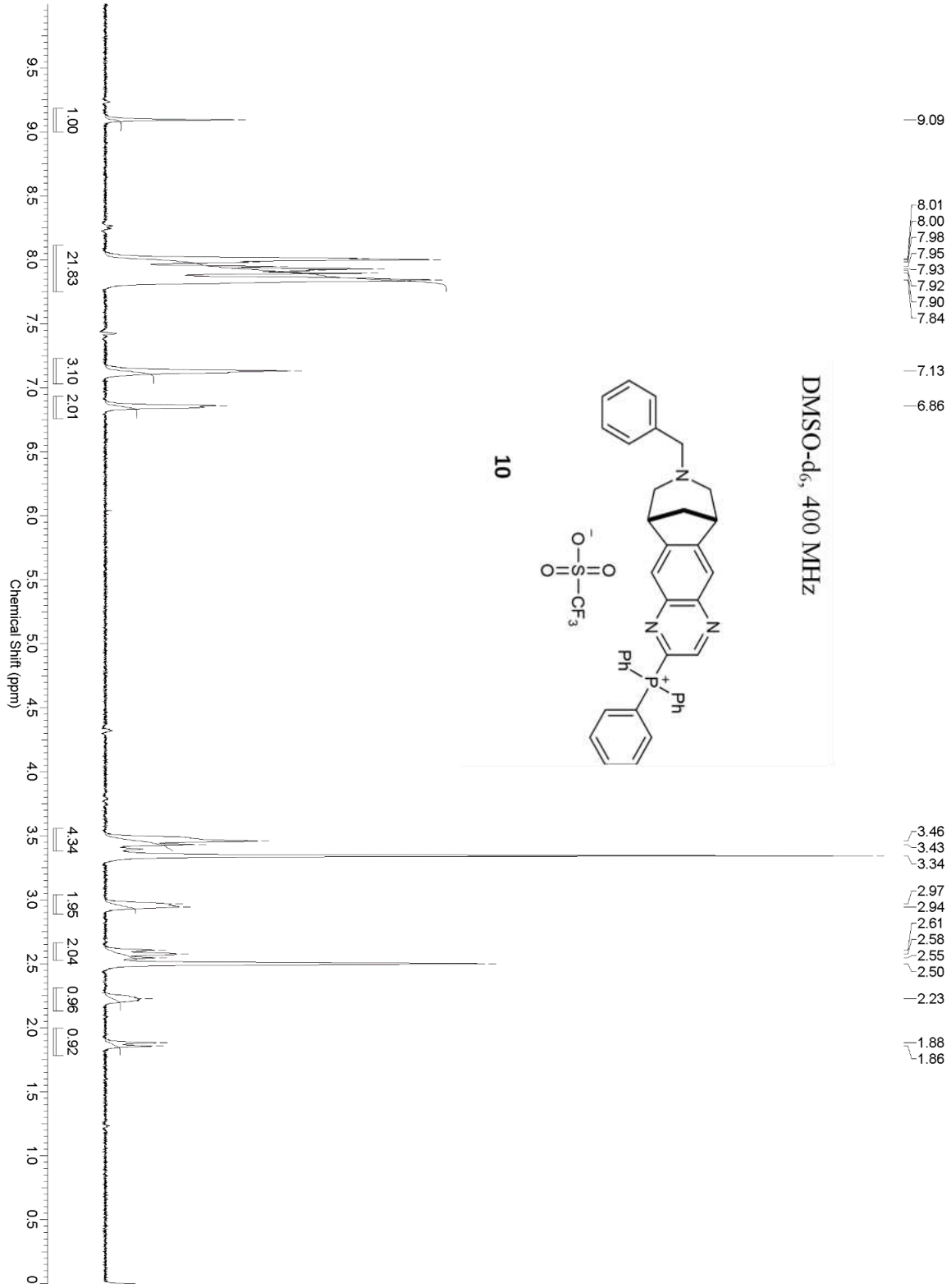

153.06
152.97
150.02
149.91
144.28
144.21
136.01
134.44
134.34
131.12
130.99
130.62
130.49
127.58
127.48
126.65
125.84
122.43
119.23
117.18
116.30
77.32
77.20
77.00
76.68
66.05
66.01
55.97
39.39
35.43
22.93
CDCl3, 100 MHz
4
Chemical Shift (ppm)

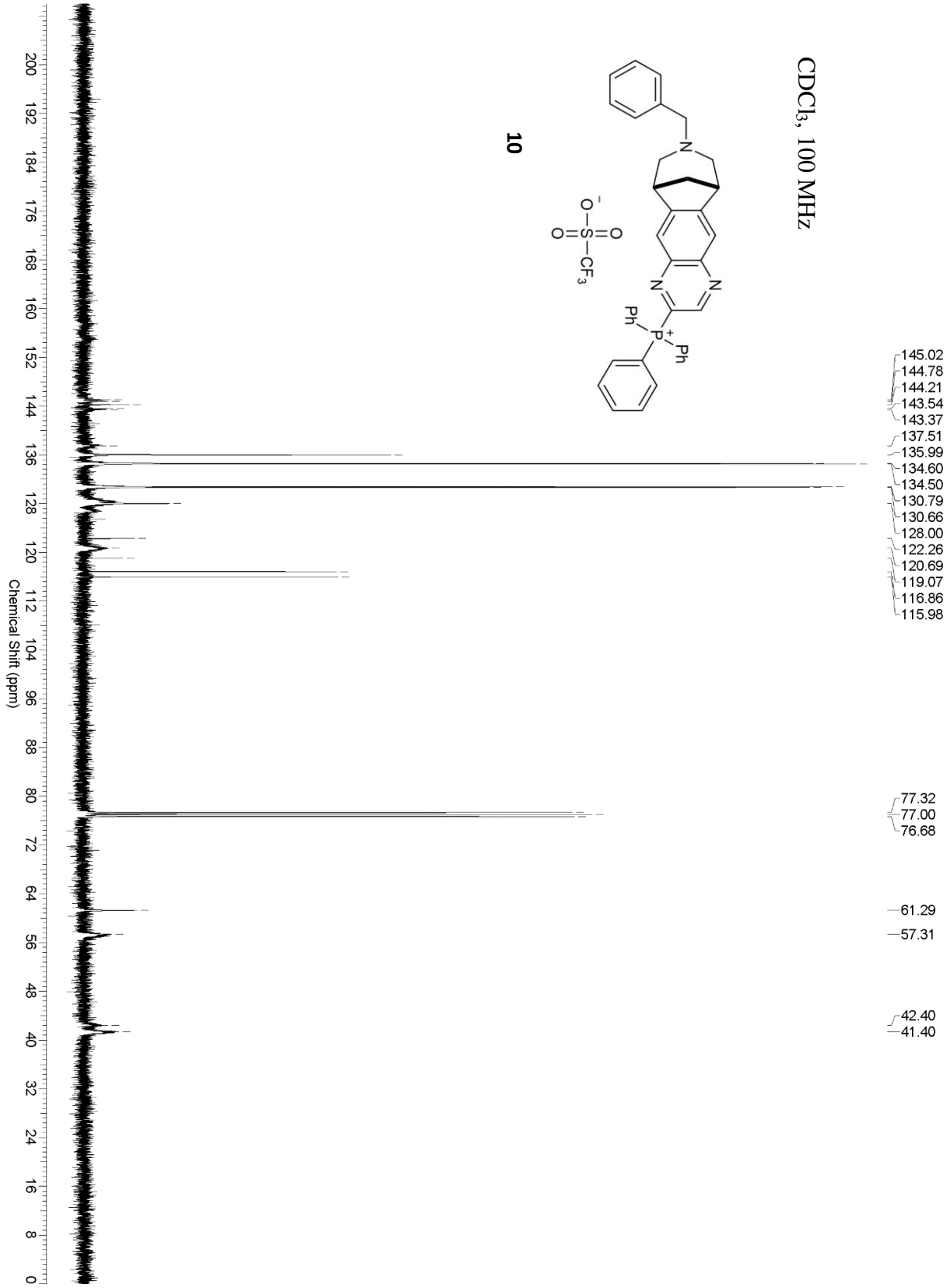

8.75
8.74
8.73
7.95
7.93
7.83
7.82
7.81
7.80
7.71
7.69
7.68
7.66
7.26
7.13
7.11
7.08
7.04
6.72
4.18
4.16
4.14
4.12
3.75
3.74
3.40
3.38
3.37
3.36
3.35
3.34
3.33
3.32
2.78
2.74
2.61
2.48
2.41
2.40
2.39
2.38
2.21
1.55
1.53
1.52
1.51
1.49
1.28
1.26
1.24
CDCl3, 400 MHz
Ph
P
Ph
Cl
N
O
S
CF3
N
O
O
Me
6
1.00
3.10
6.26
6.30
3.06
0.98
2.06
1.95
3.07
1.00
0.99
3.05
0.82
0.97
3.32
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

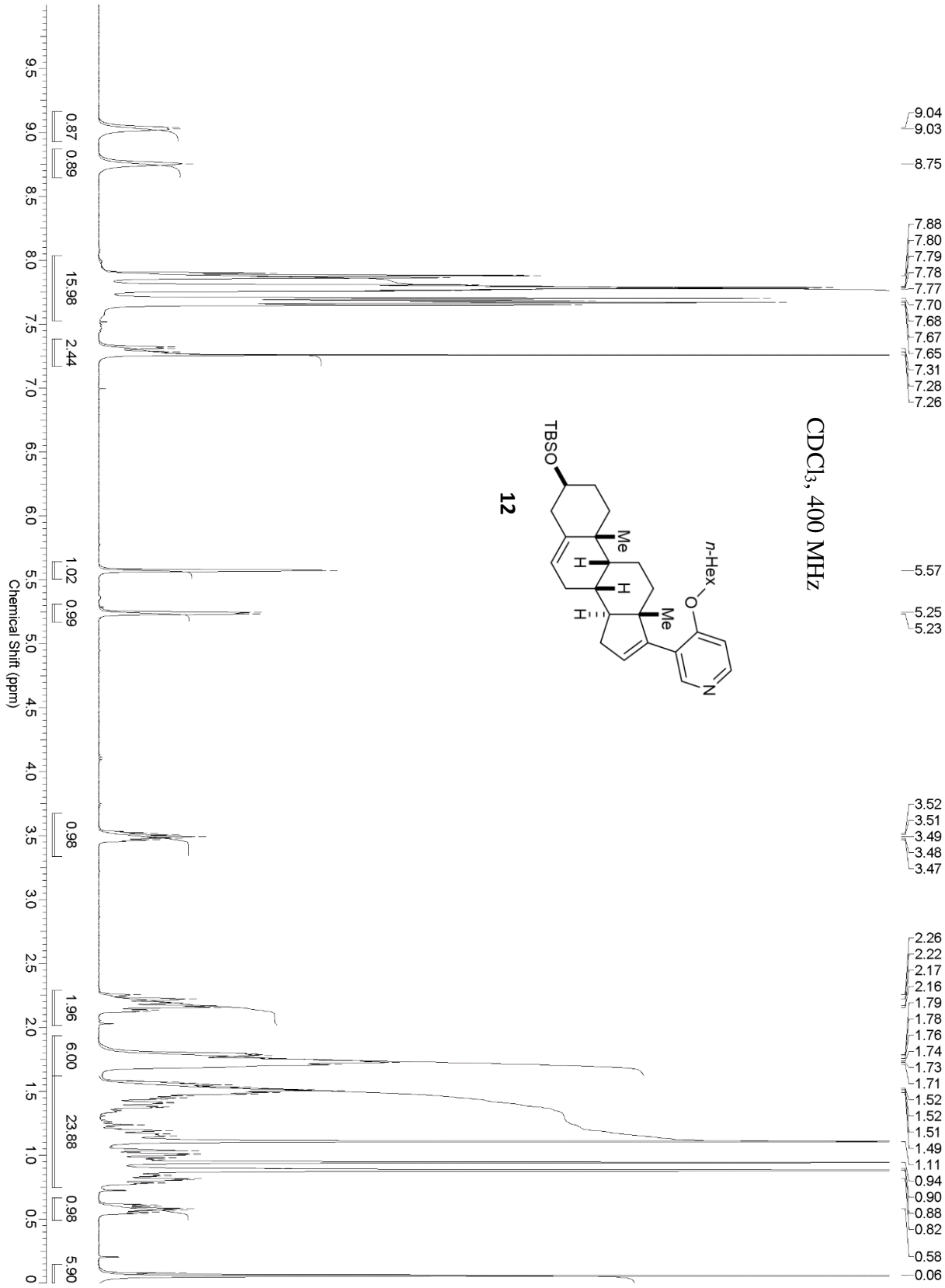

CDCl3, 100 MHz
6
Cl
N
O
O
N
Me
Ph
P
+
Ph
O
O
S
O
CF3
-
163.68
163.60
155.37
149.14
149.03
139.23
136.84
136.08
136.05
134.27
134.16
133.57
131.58
131.20
131.07
129.85
126.43
122.38
119.18
116.86
115.98
77.32
77.20
77.00
76.68
61.39
44.65
44.41
30.74
30.46
30.39
29.39
14.59
Chemical Shift (ppm)

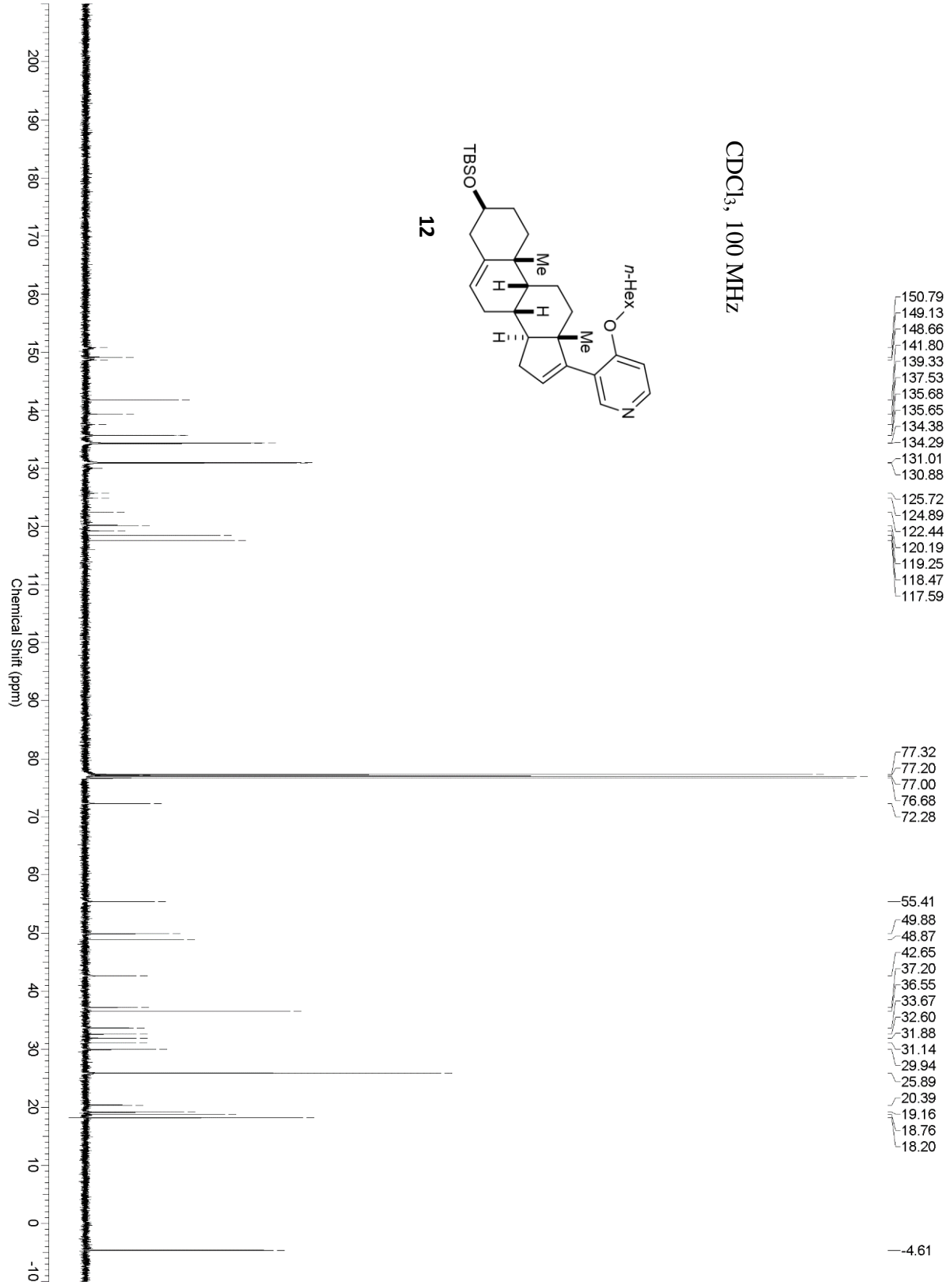

8.98
8.97
8.95
7.90
7.76
7.75
7.74
7.73
7.59
7.58
7.56
7.55
7.53
7.26
7.22
7.22
4.30
4.28
4.27
2.50
2.48
2.23
2.22
2.21
2.18
2.18
1.00
3.12
6.52
6.44
1.11
5.15
1.01
0.98
9.27
Chemical Shift (ppm)
CDCl3, 400 MHz
8

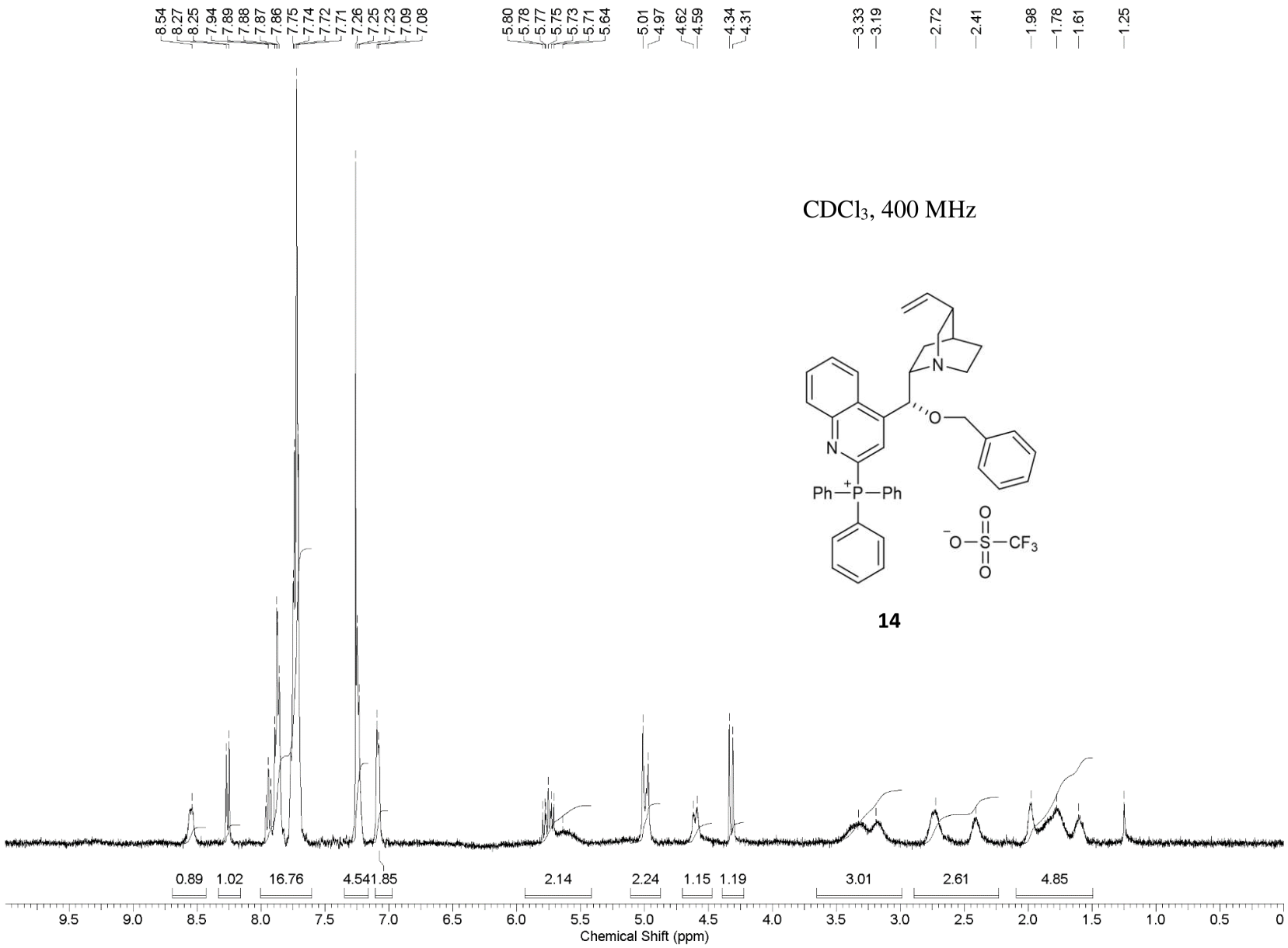

CDCl3, 100 MHz
8
Chemical Shift (ppm)
165.60
165.50
151.01
150.92
140.26
135.80
134.07
133.96
132.25
130.67
130.54
129.34
128.49
127.92
126.24
124.38
122.06
118.86
115.75
114.86
77.32
77.00
76.67
56.73
49.77
44.88
31.99

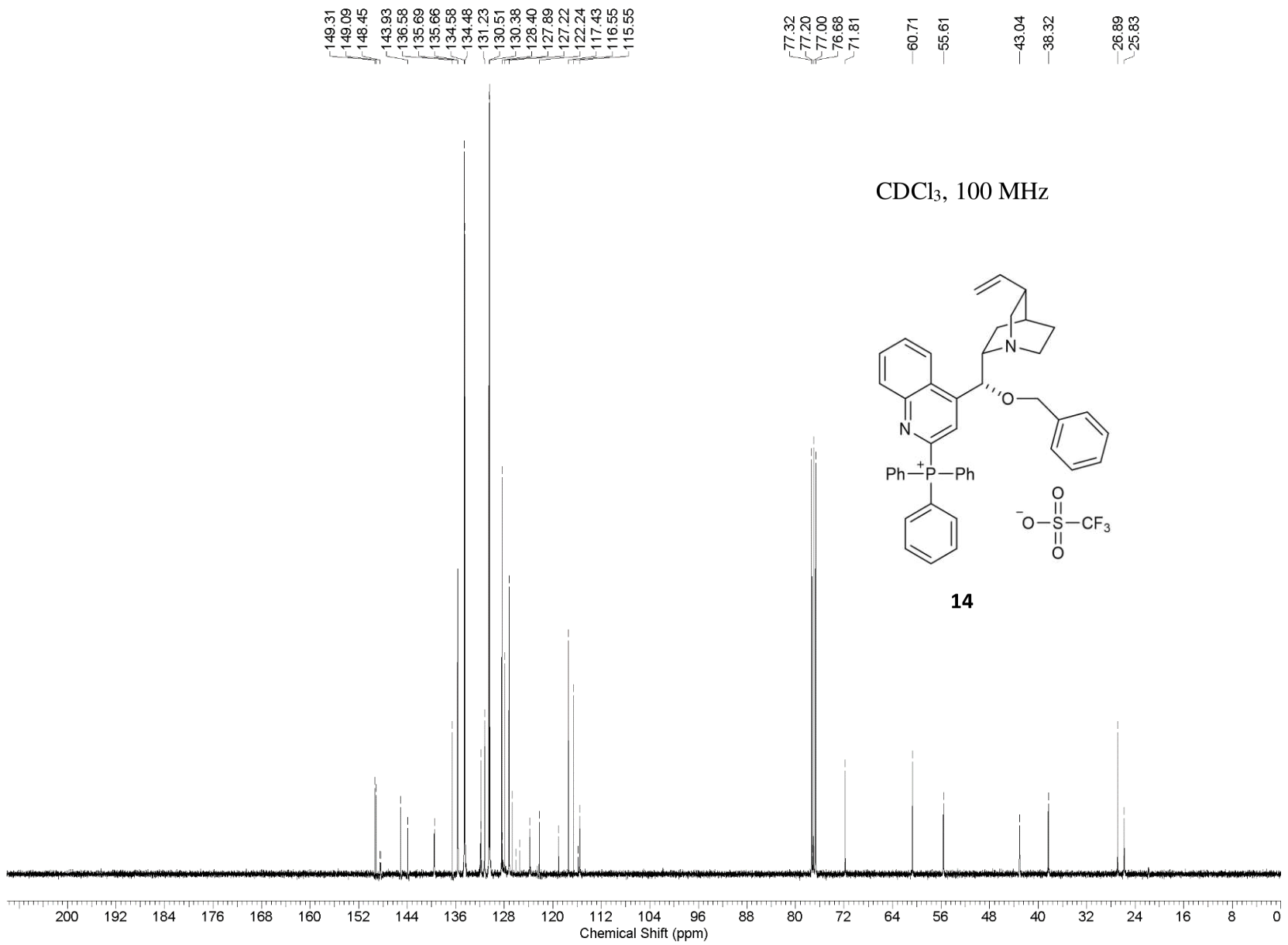

DMSO-d6, 400 MHz
10
9.09
8.01
8.00
7.98
7.95
7.93
7.92
7.90
7.84
7.13
6.86
3.46
3.43
3.34
2.97
2.94
2.61
2.58
2.55
2.50
2.23
1.88
1.86
1.00
21.83
3.10
2.01
4.34
1.95
2.04
0.96
0.92
Chemical Shift (ppm)

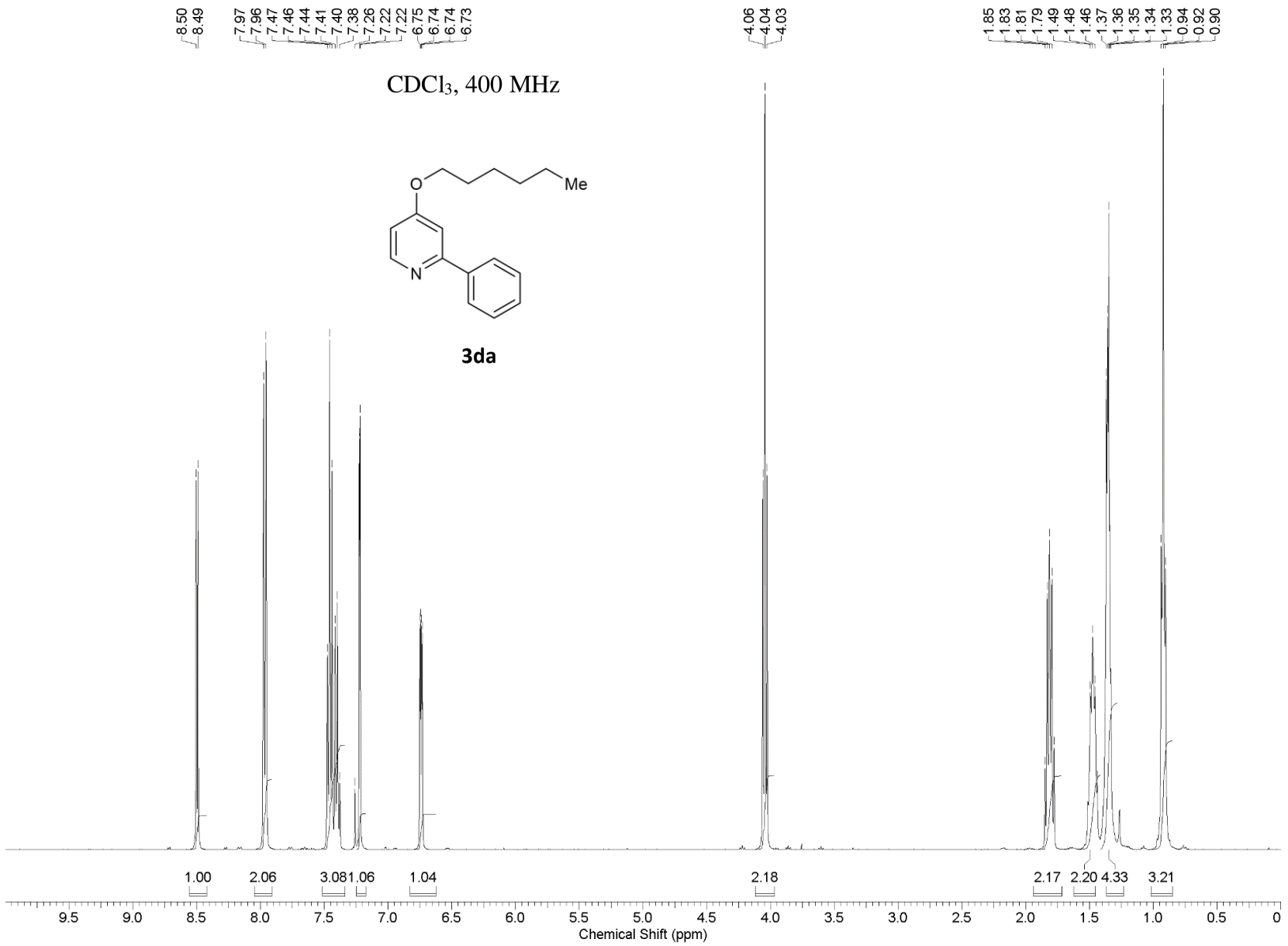

CDCl3, 100 MHz
10
145.02
144.78
144.21
143.54
143.37
137.51
135.99
134.60
134.50
130.79
130.66
128.00
122.26
120.69
119.07
116.86
115.98
77.32
77.00
76.68
61.29
57.31
42.40
41.40
Chemical Shift (ppm)

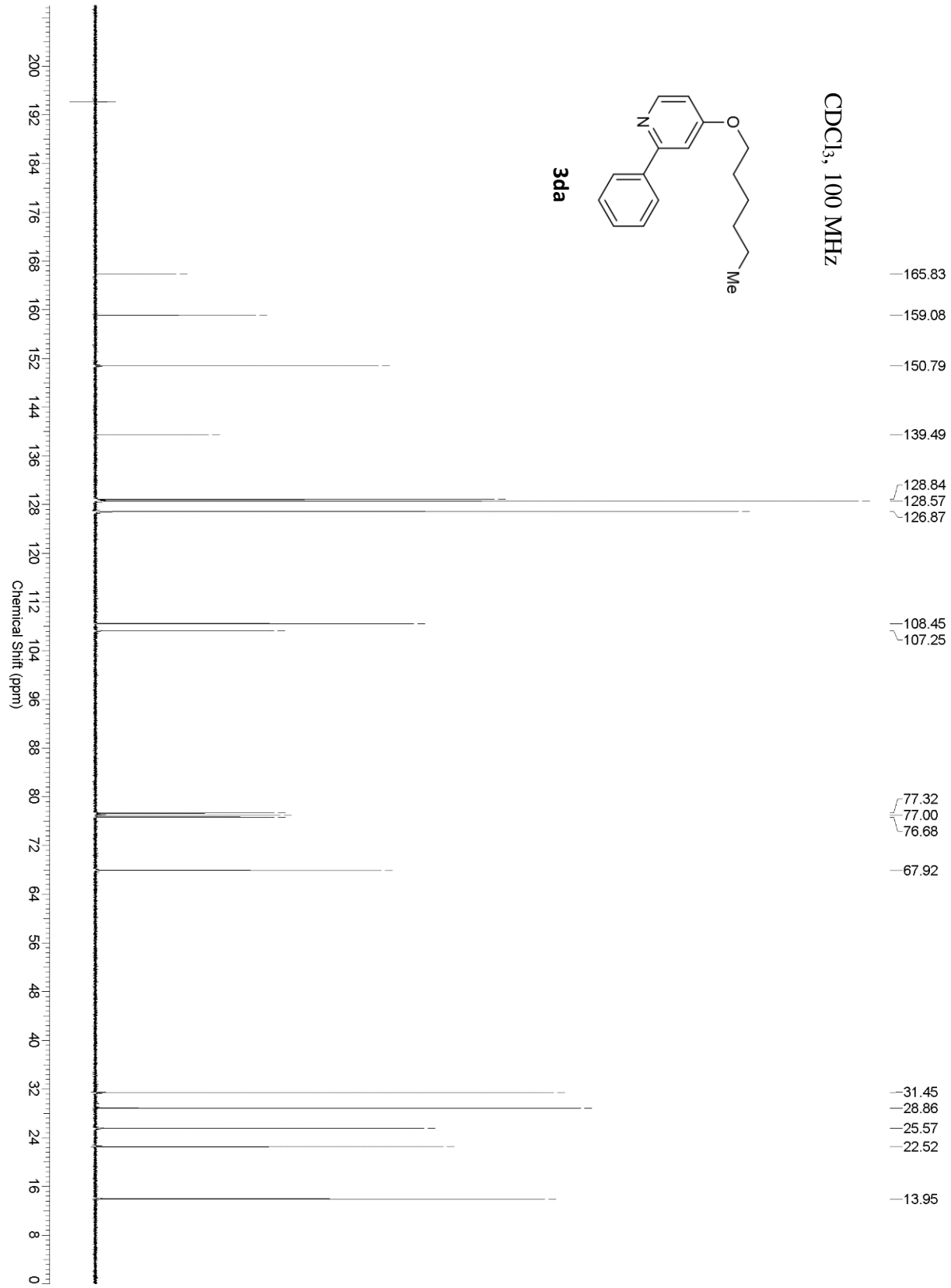

CDCl3, 400 MHz
12
TBSO
Me
H
H
H
Me
n-Hex
O
N
9.04
9.03
8.75
7.88
7.80
7.79
7.78
7.77
7.70
7.68
7.67
7.65
7.31
7.28
7.26
5.57
5.25
5.23
3.52
3.51
3.49
3.48
3.47
2.26
2.22
2.17
2.16
1.79
1.78
1.76
1.74
1.73
1.71
1.52
1.52
1.51
1.49
1.11
0.94
0.90
0.88
0.82
0.58
0.06
0.87
0.89
15.98
2.44
1.02
0.99
0.98
1.96
6.00
23.88
0.98
5.90
Chemical Shift (ppm)

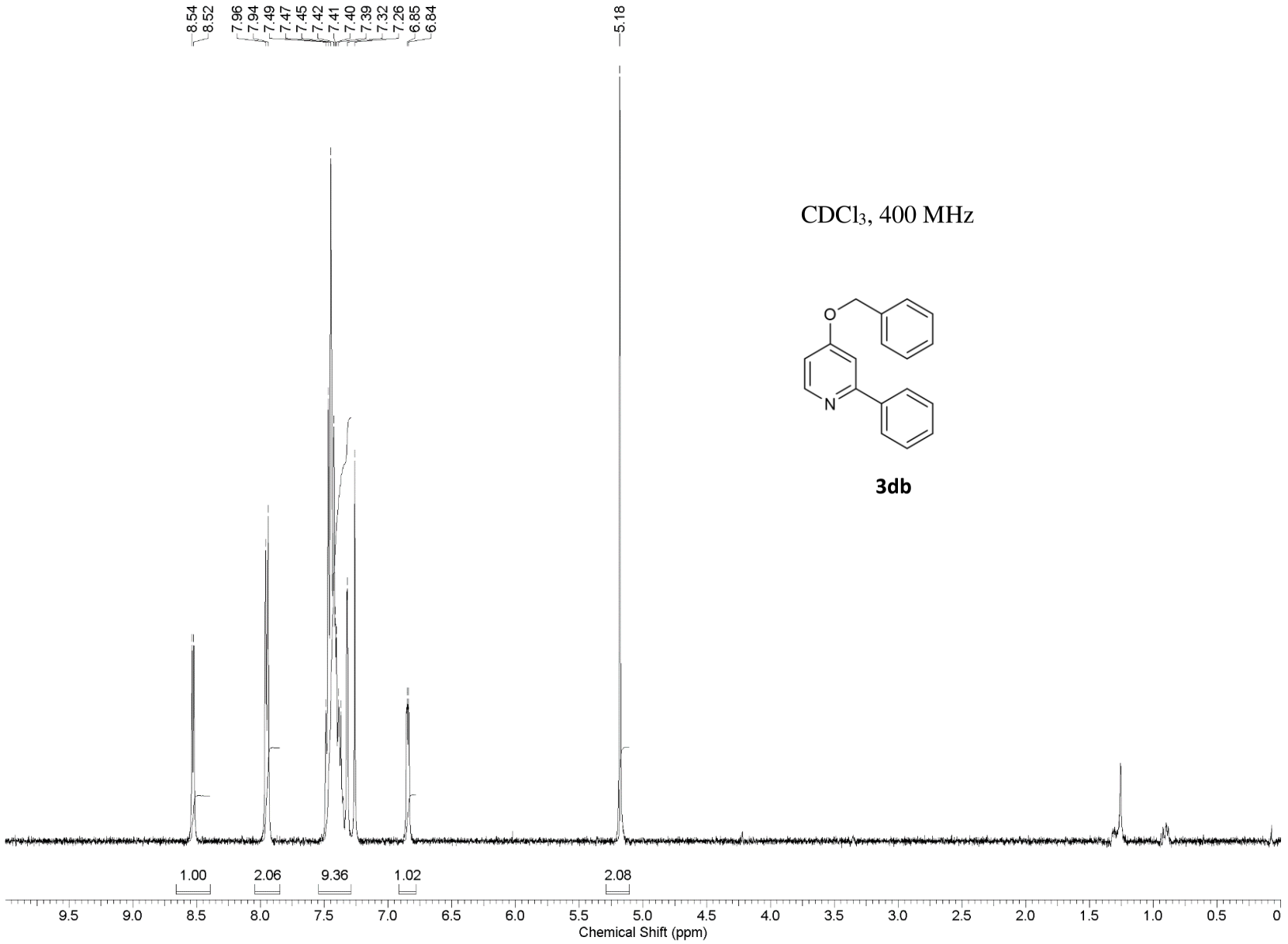

CDCl3, 100 MHz
12
TBSO
Me
H
H
H
Me
n-Hex
O
N
150.79
149.13
148.66
141.80
139.33
137.53
135.68
135.65
134.38
134.29
131.01
130.88
125.72
124.89
122.44
120.19
119.25
118.47
117.59
77.32
77.20
77.00
76.68
72.28
55.41
49.88
48.87
42.65
37.20
36.55
33.67
32.60
31.88
31.14
29.94
25.89
20.39
19.16
18.76
18.20
-4.61
Chemical Shift (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


8.54
8.27
8.25
7.94
7.89
7.88
7.87
7.86
7.75
7.74
7.72
7.71
7.26
7.25
7.23
7.09
7.08
5.80
5.78
5.77
5.75
5.73
5.71
5.64
5.01
4.97
4.62
4.59
4.34
4.31
3.33
3.19
2.72
2.41
1.98
1.78
1.61
1.25
CDCl3, 400 MHz
N
O
N
Ph—P—Ph
O—S—CF3
O
O
O
14
0.89
1.02
16.76
4.54
1.85
2.14
2.24
1.15
1.19
3.01
2.61
4.85
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


149.31
149.09
148.45
143.93
136.58
135.69
135.66
134.58
134.48
131.23
130.51
130.38
128.40
127.89
127.22
122.24
117.43
116.55
115.55
77.32
77.20
77.00
76.68
71.81
60.71
55.61
43.04
38.32
26.89
25.83
CDCl3, 100 MHz
Ph—P—Ph
O—S—CF3
14
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

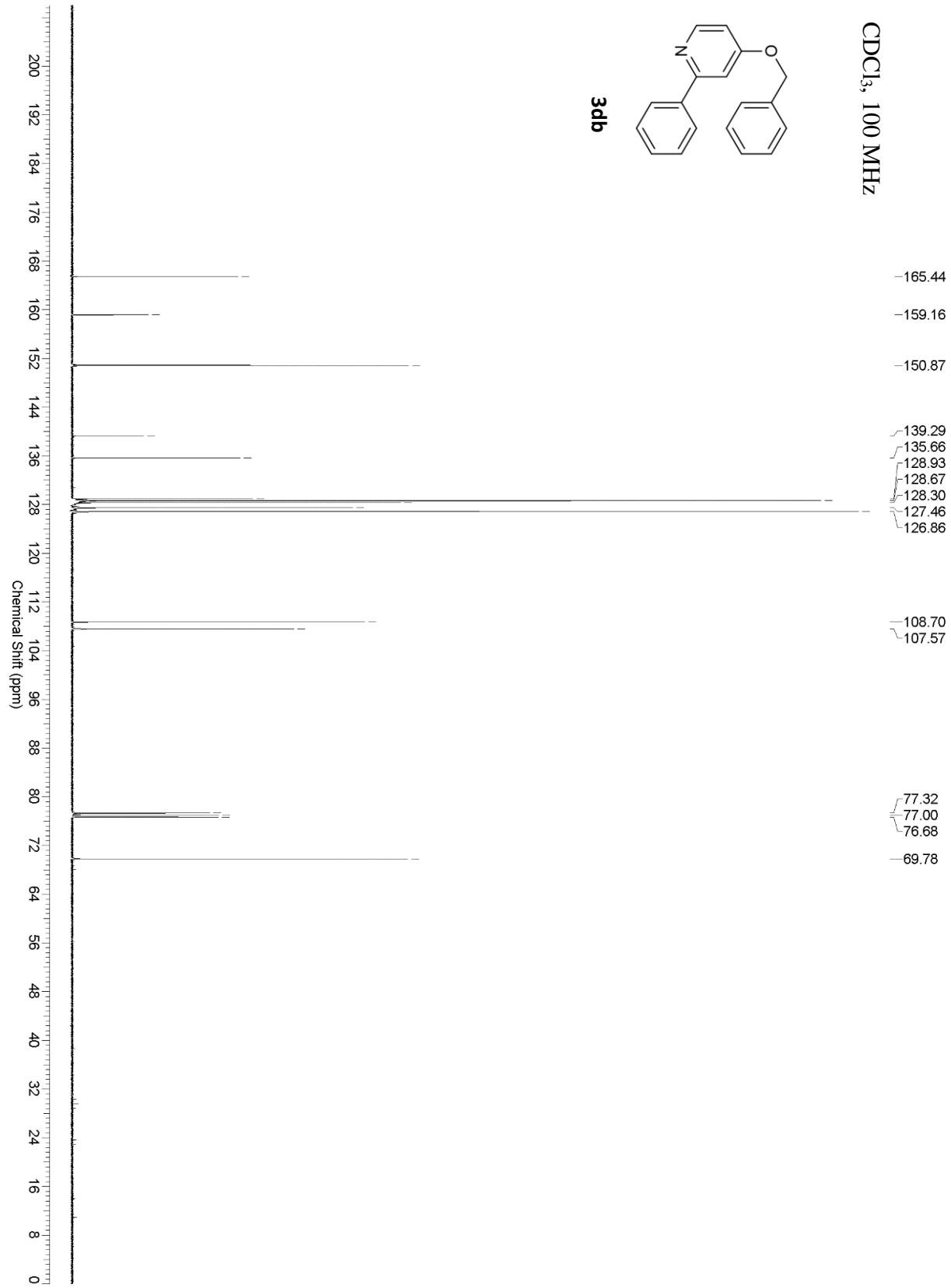

8.50
8.49
7.97
7.96
7.47
7.46
7.44
7.41
7.40
7.38
7.26
7.22
6.75
6.74
6.74
6.73
4.06
4.04
4.03
1.85
1.83
1.81
1.79
1.49
1.48
1.46
1.37
1.36
1.35
1.34
1.33
0.94
0.92
0.90
CDCl3, 400 MHz
O
Me
N
3da
1.00
2.06
3.08
1.06
1.04
2.18
2.17
2.20
4.33
3.21
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

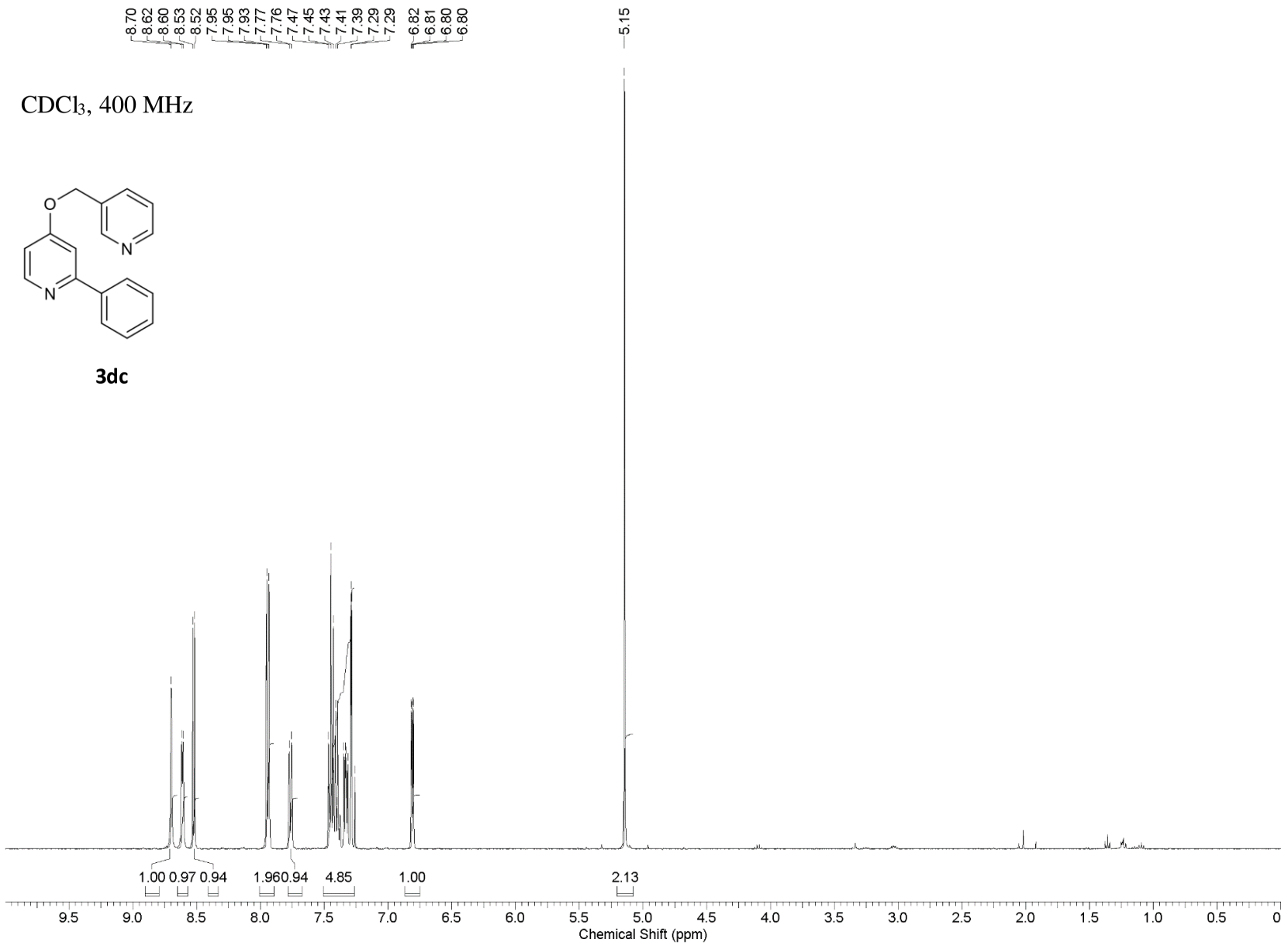

CDCl3, 100 MHz
3da
N
O
Me
165.83
159.08
150.79
139.49
128.84
128.57
126.87
108.45
107.25
77.32
77.00
76.68
67.92
31.45
28.86
25.57
22.52
13.95
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

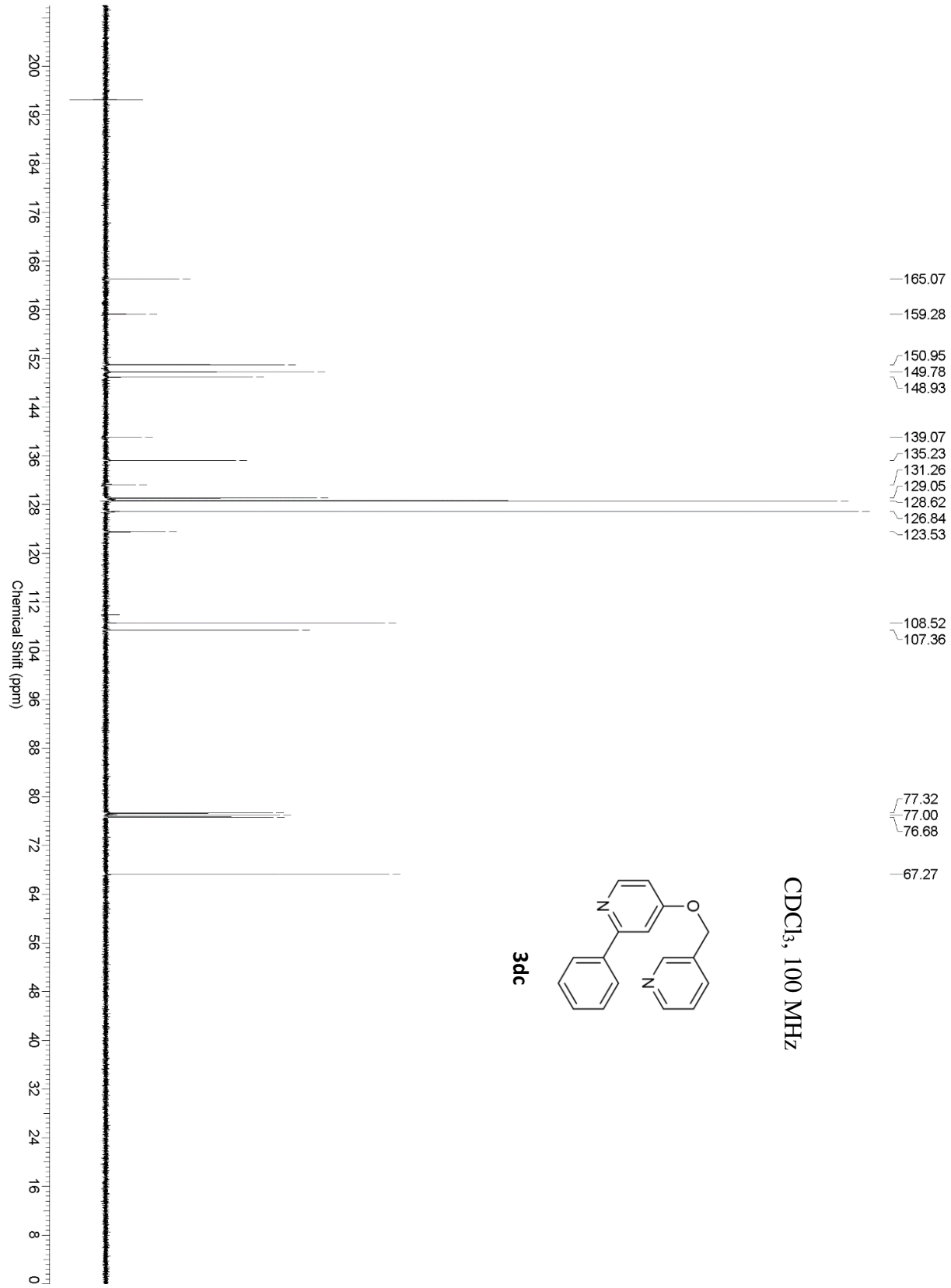


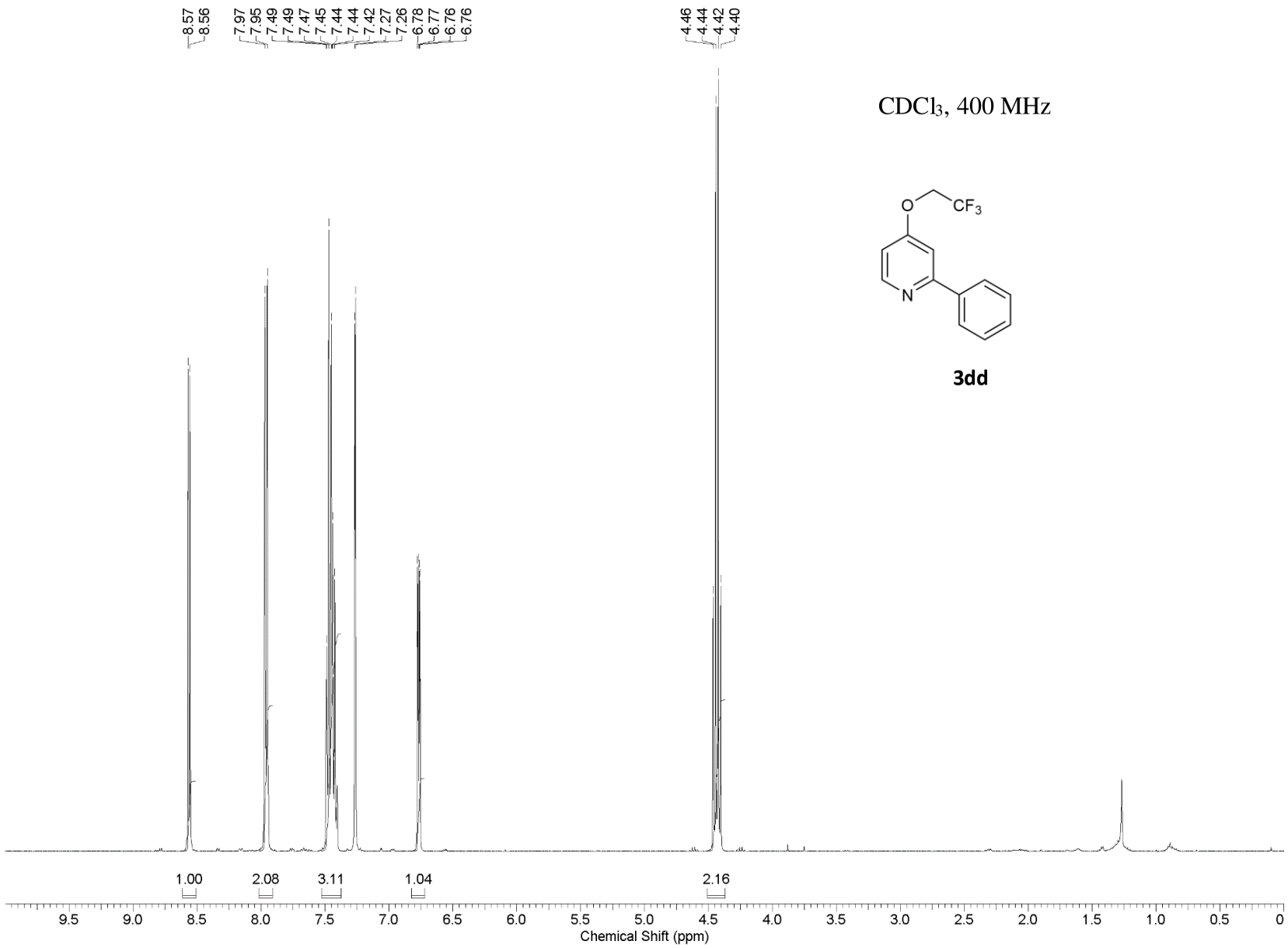
$CDCl_3$, 400 MHz

3db


CDCl3, 100 MHz
3db
N
O
165.44
159.16
150.87
139.29
135.66
128.93
128.67
128.30
127.46
126.86
108.70
107.57
77.32
77.00
76.68
69.78
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

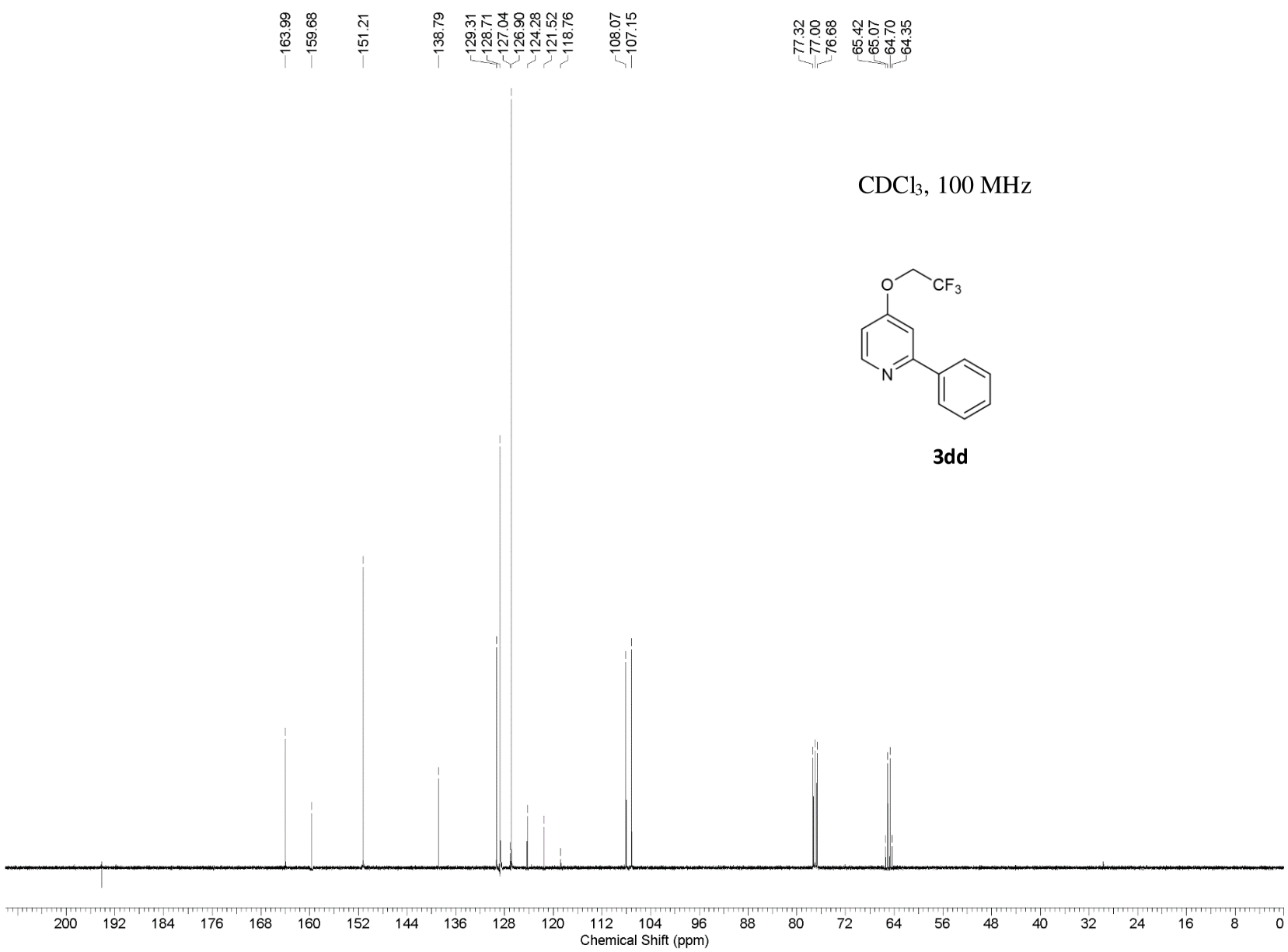

8.70
8.62
8.60
8.53
8.52
7.95
7.93
7.77
7.76
7.47
7.45
7.43
7.41
7.39
7.29
7.29
6.82
6.81
6.80
6.80
5.15
CDCl3, 400 MHz
O
N
N
3dc
1.00 0.97 0.94 1.96 0.94 4.85 1.00 2.13
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


165.07
159.28
150.95
149.78
148.93
139.07
135.23
131.26
129.05
128.62
126.84
123.53
108.52
107.36
77.32
77.00
76.68
67.27
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
CDCl3, 100 MHz
3dc
N
O
N



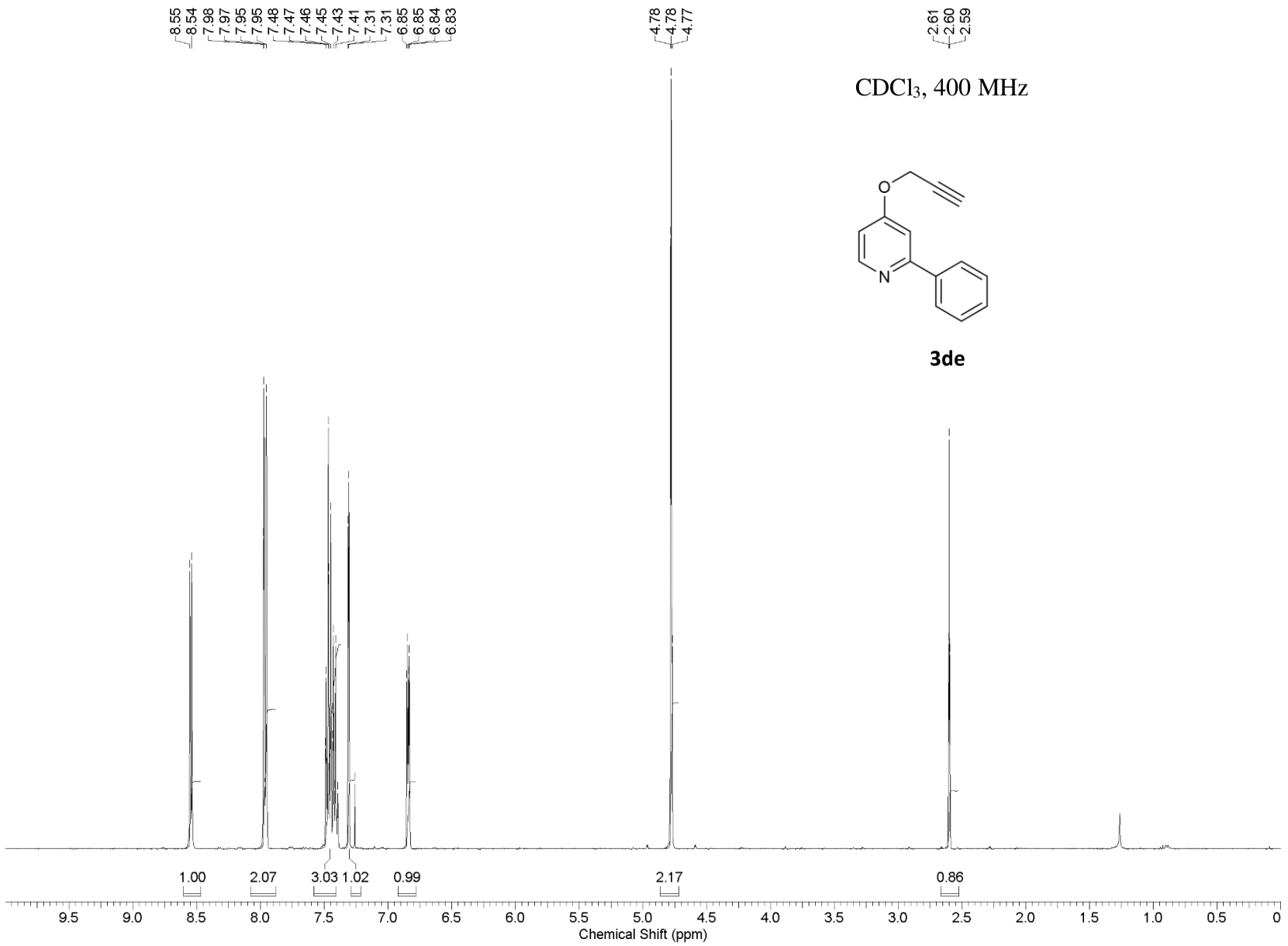
$CDCl_3$, 400 MHz

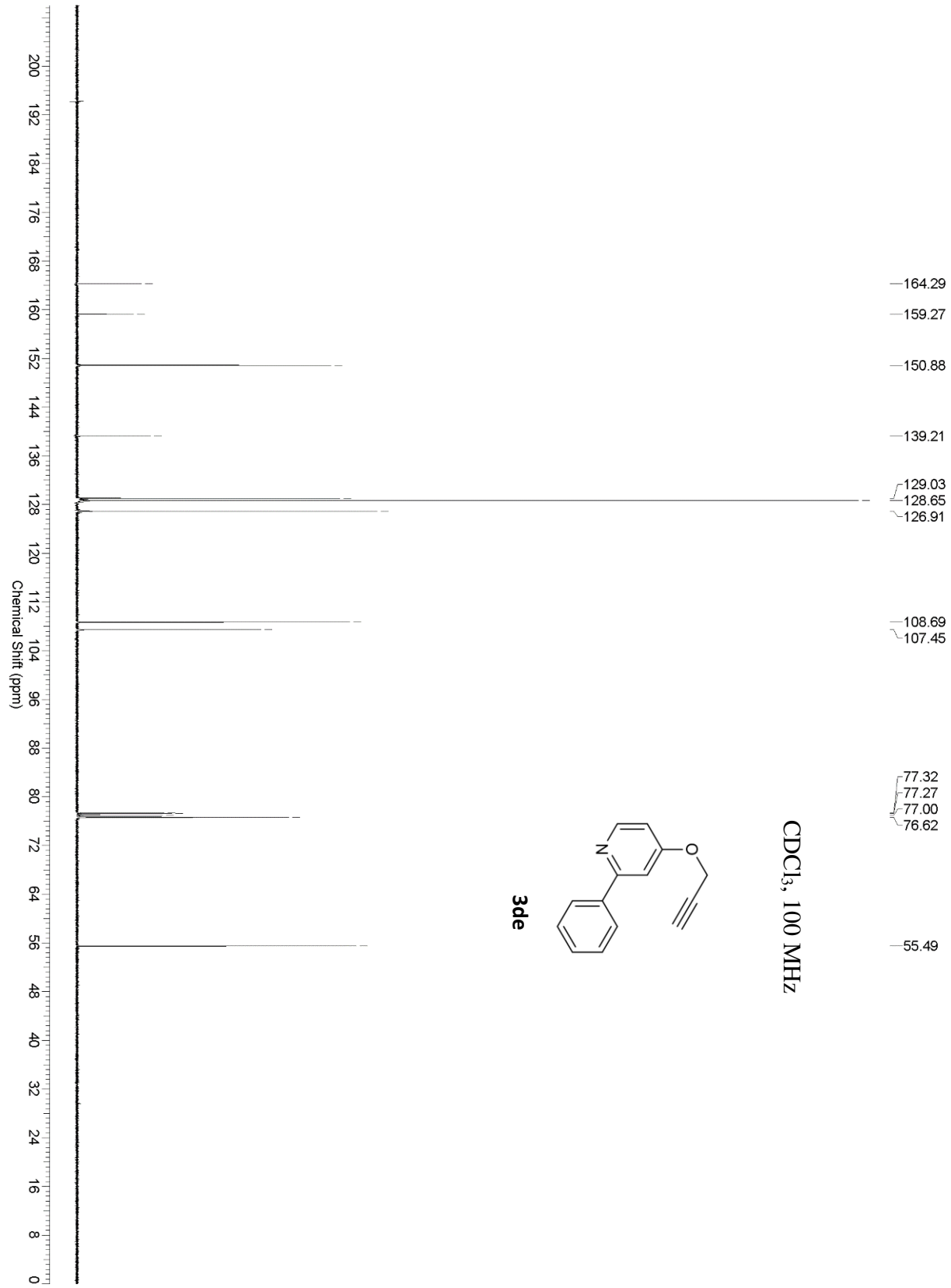
3dd

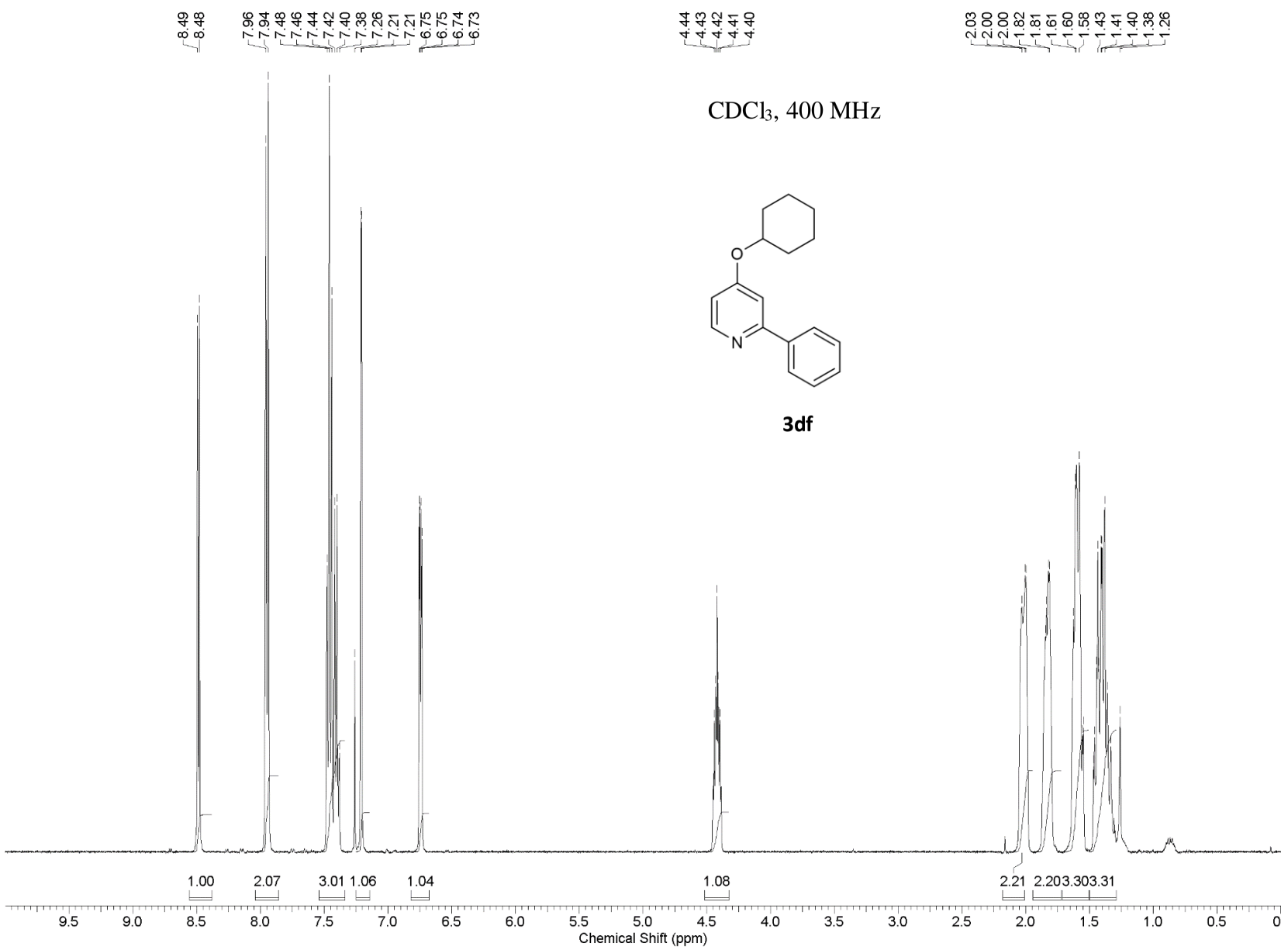


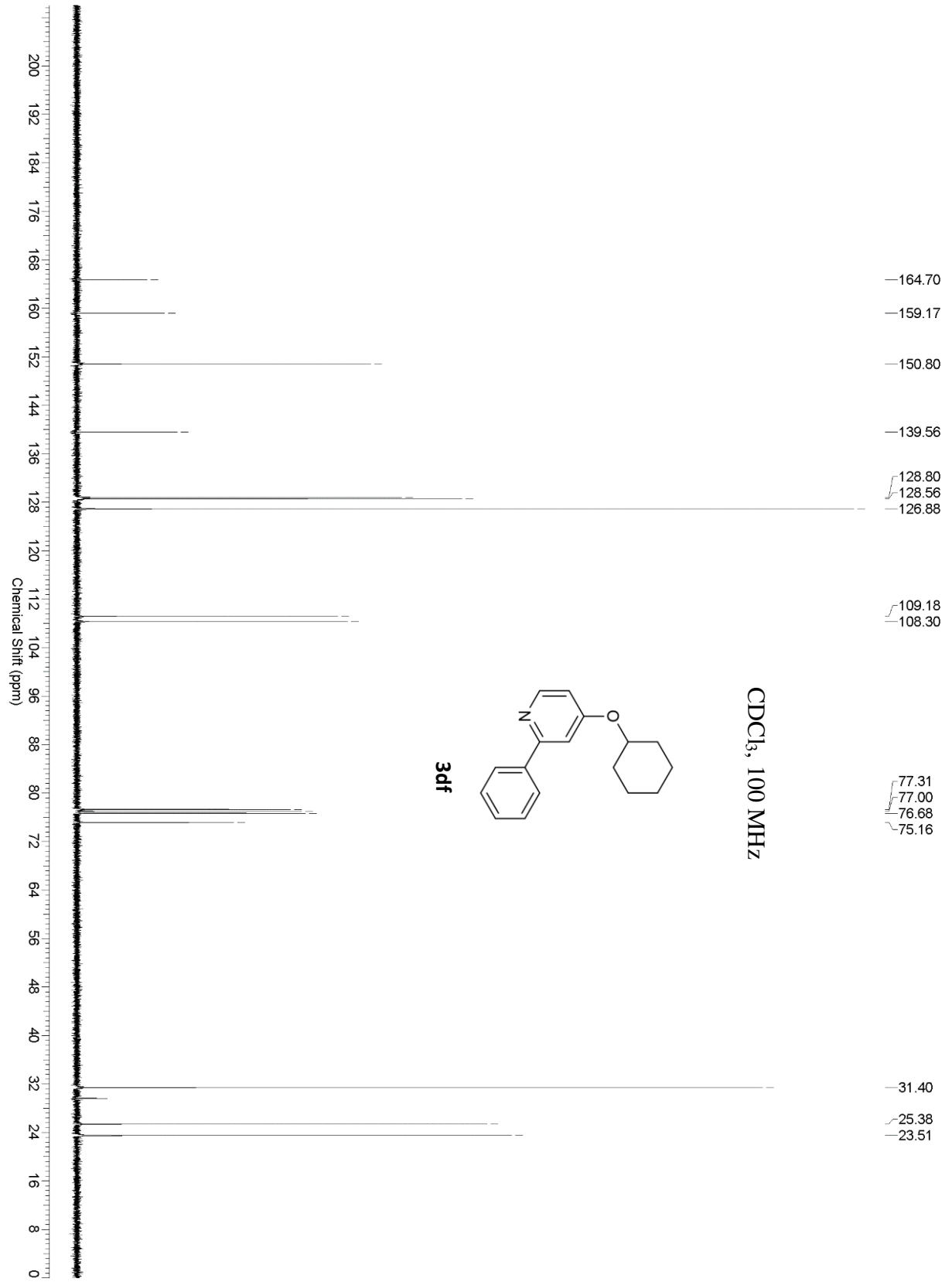
$CDCl_3$, 100 MHz

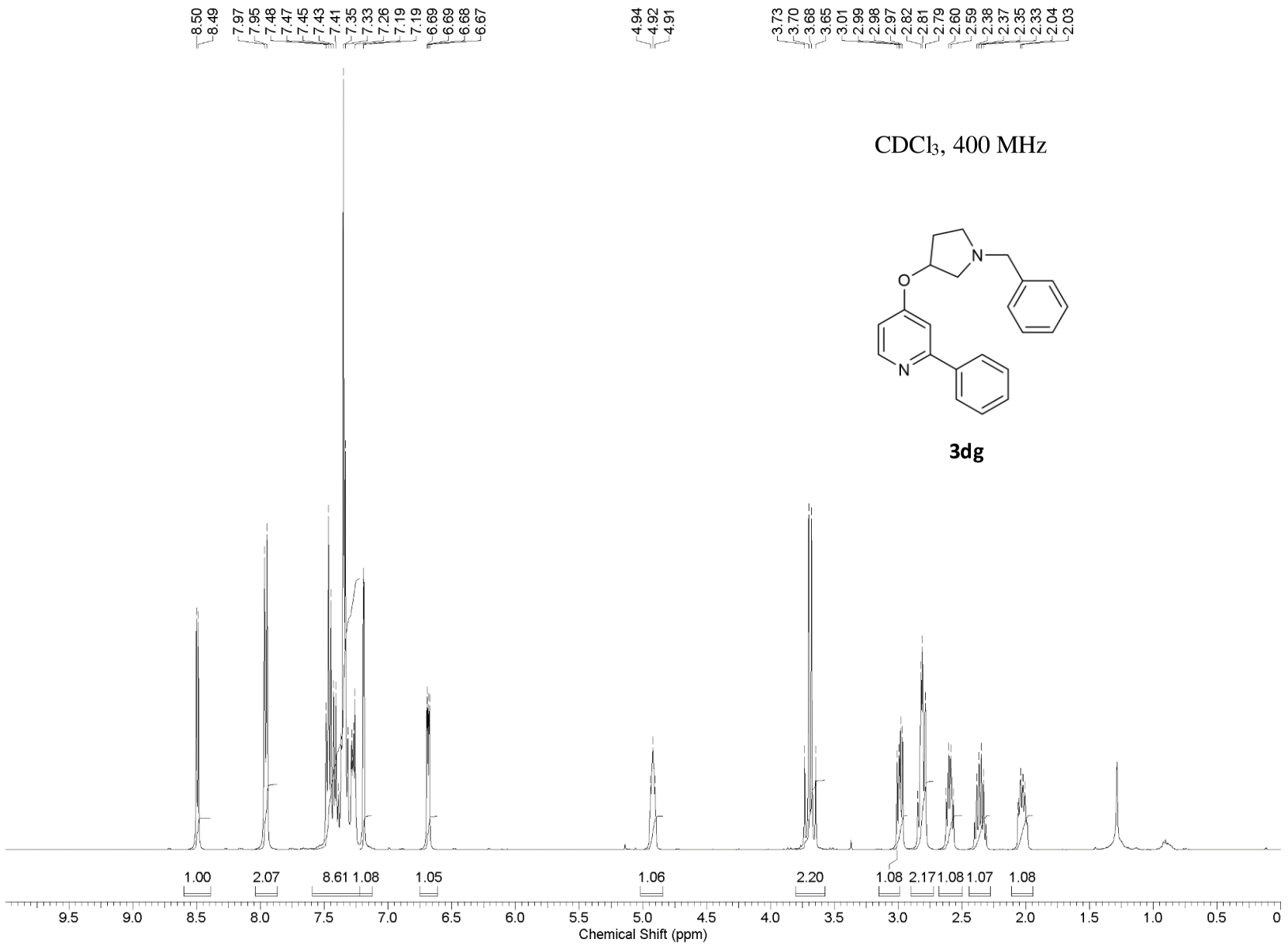
3dd

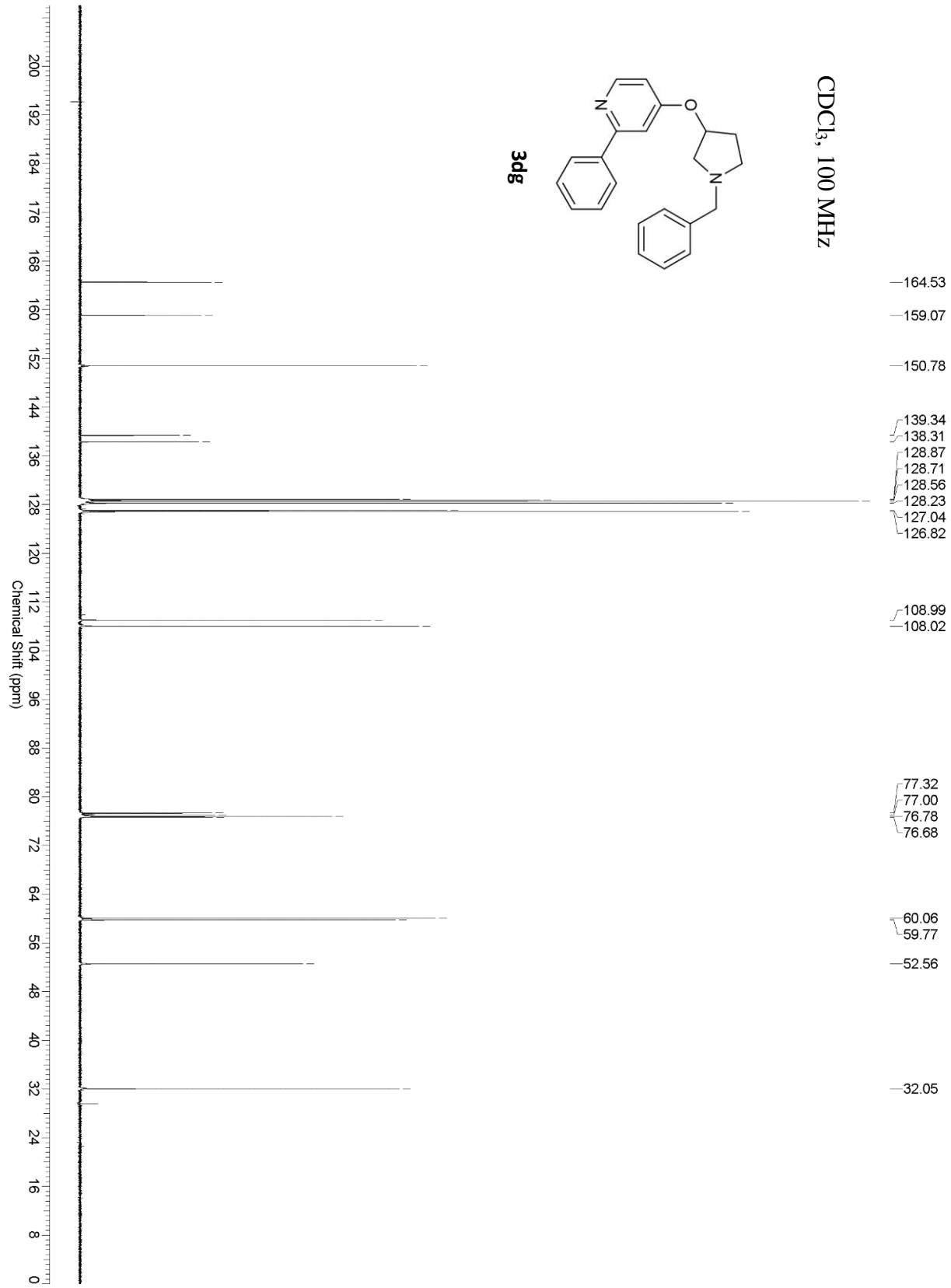

8.55
8.54
7.98
7.97
7.95
7.95
7.48
7.47
7.46
7.45
7.43
7.41
7.31
7.31
6.85
6.85
6.84
6.83
4.78
4.78
4.77
2.61
2.60
2.59
CDCl3, 400 MHz
O
N
3de
1.00
2.07
3.03
1.02
0.99
2.17
0.86
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

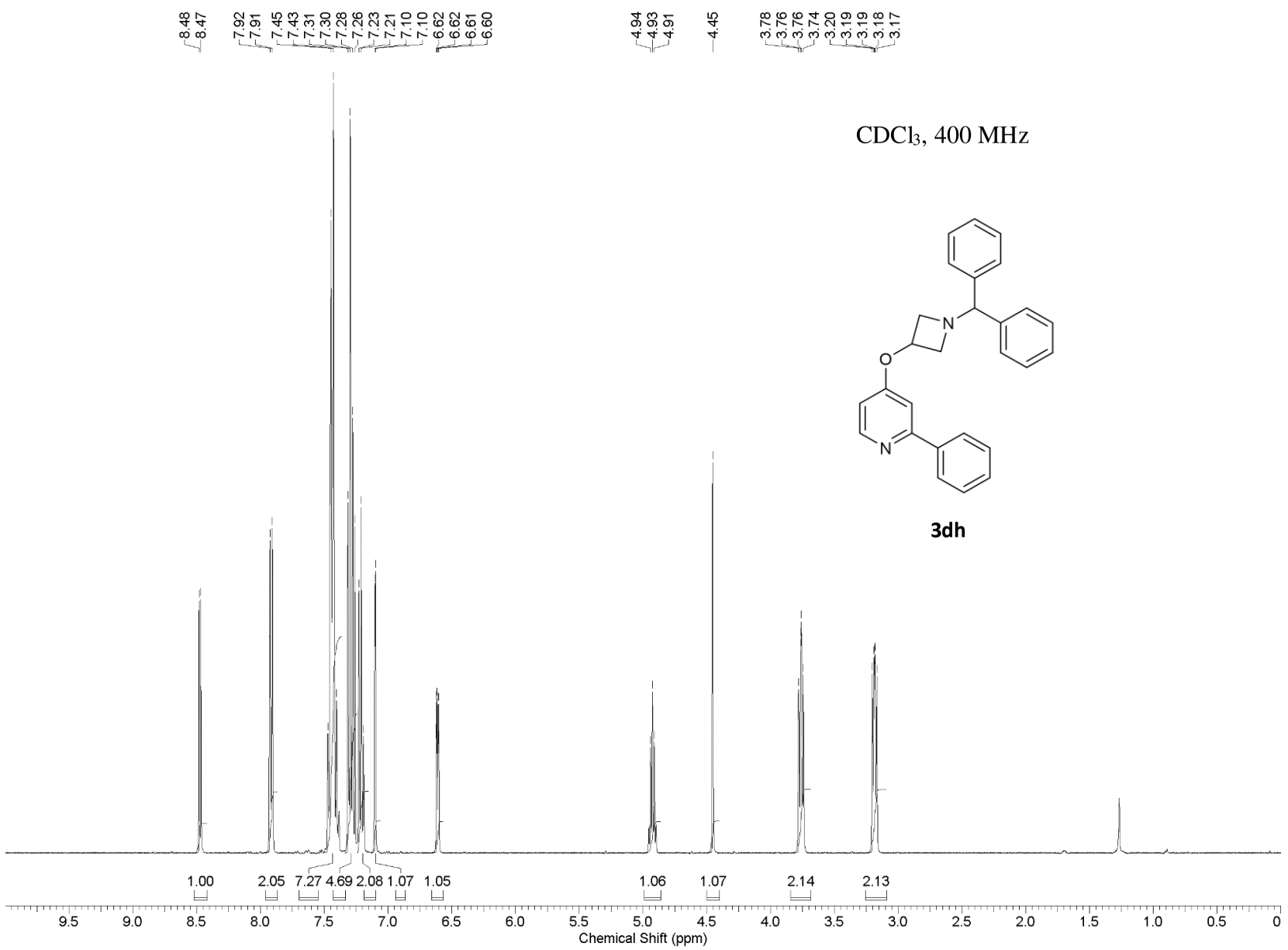

164.29
159.27
150.88
139.21
129.03
128.65
126.91
108.69
107.45
77.32
77.27
77.00
76.62
55.49
CDCl3, 100 MHz
3de
N
O
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

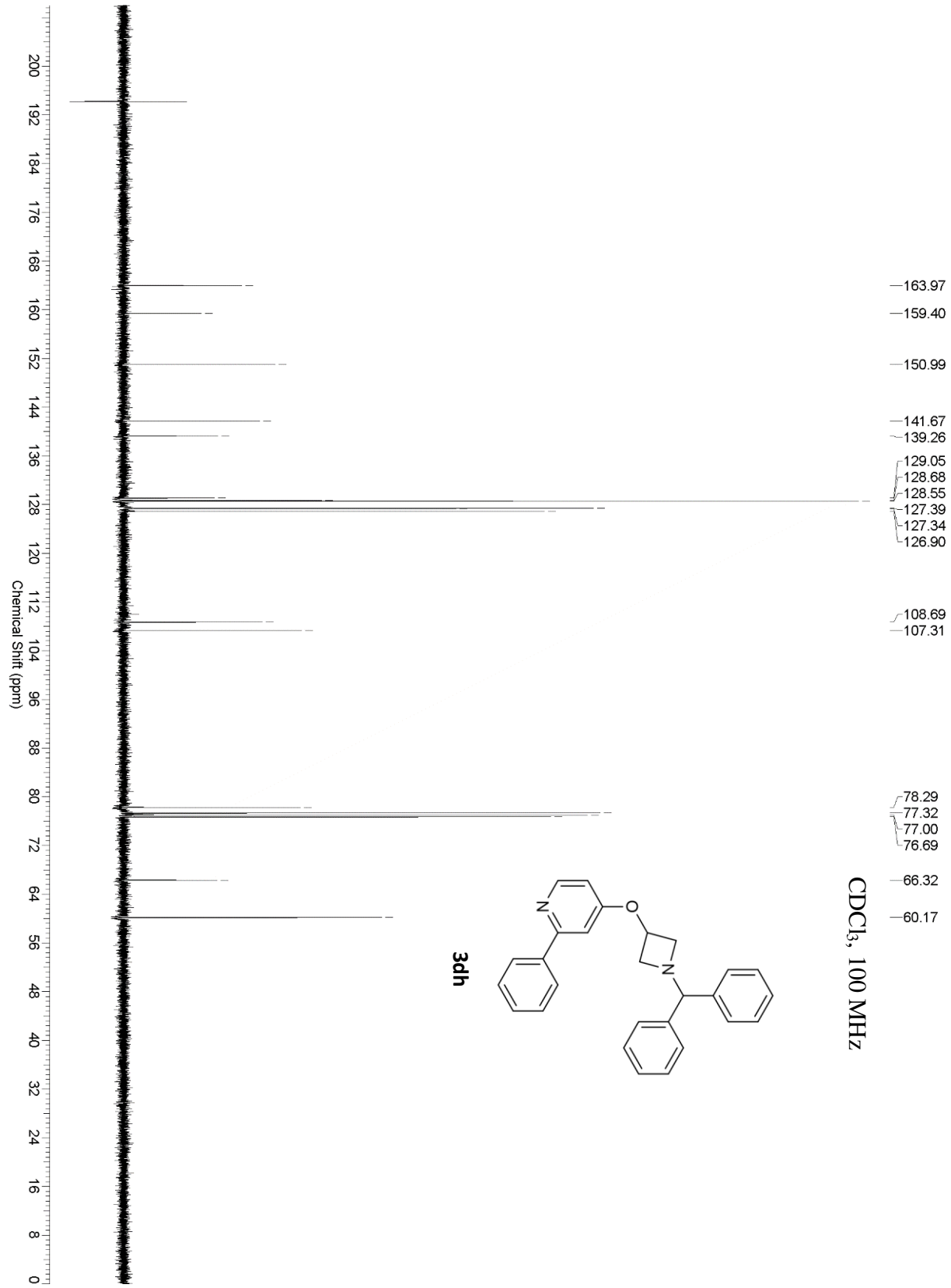

8.49
8.48
7.96
7.94
7.48
7.46
7.44
7.42
7.40
7.38
7.26
7.21
7.21
6.75
6.75
6.74
6.73
4.44
4.43
4.42
4.41
4.40
2.03
2.00
2.00
1.82
1.81
1.61
1.60
1.58
1.43
1.41
1.40
1.38
1.26
CDCl3, 400 MHz
O
N
3df
1.00
2.07
3.01
1.06
1.04
1.08
2.21
2.20
3.30
3.31
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

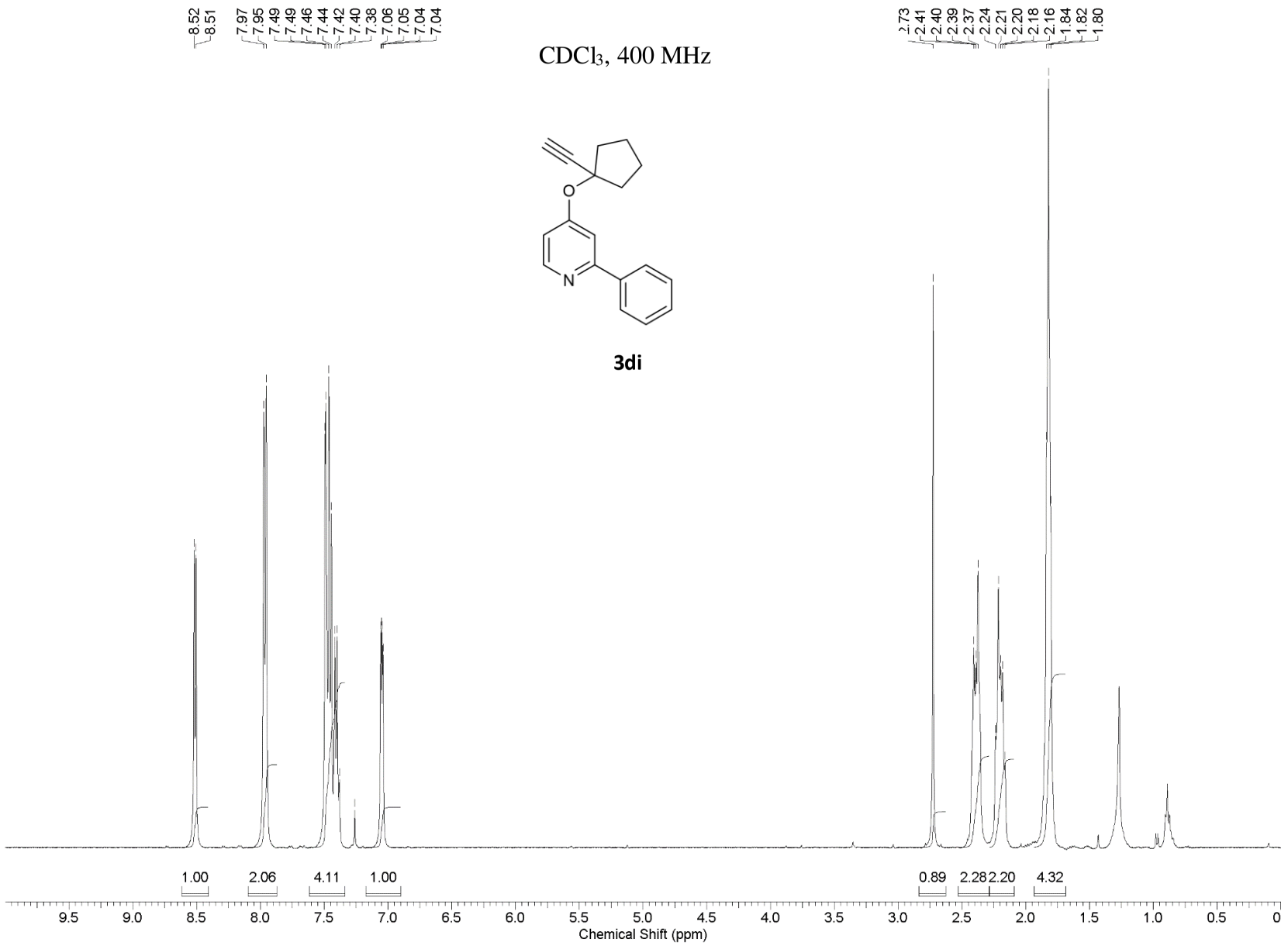

164.70
159.17
150.80
139.56
128.80
128.56
126.88
109.18
108.30
77.31
77.00
76.68
75.16
31.40
25.38
23.51
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
3df
CDCl3, 100 MHz

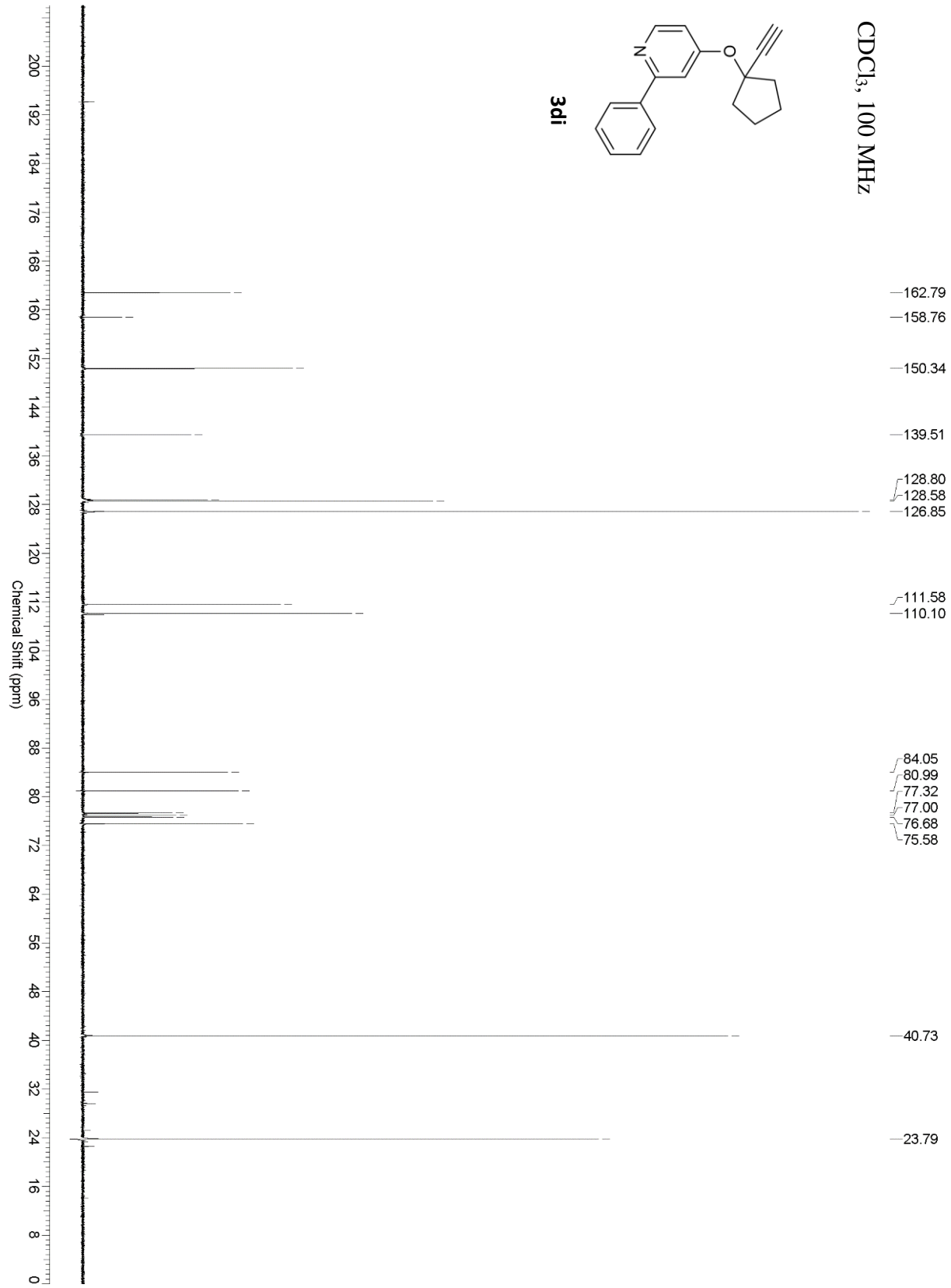

8.50
8.49
7.97
7.95
7.48
7.47
7.45
7.43
7.41
7.35
7.33
7.26
7.19
7.19
6.69
6.69
6.68
6.67
4.94
4.92
4.91
3.73
3.70
3.68
3.65
3.01
2.99
2.98
2.97
2.82
2.81
2.79
2.60
2.59
2.38
2.37
2.35
2.33
2.04
2.03
CDCl3, 400 MHz
O
N
N
3dg
1.00
2.07
8.61
1.08
1.05
1.06
2.20
1.08
2.17
1.08
1.07
1.08
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

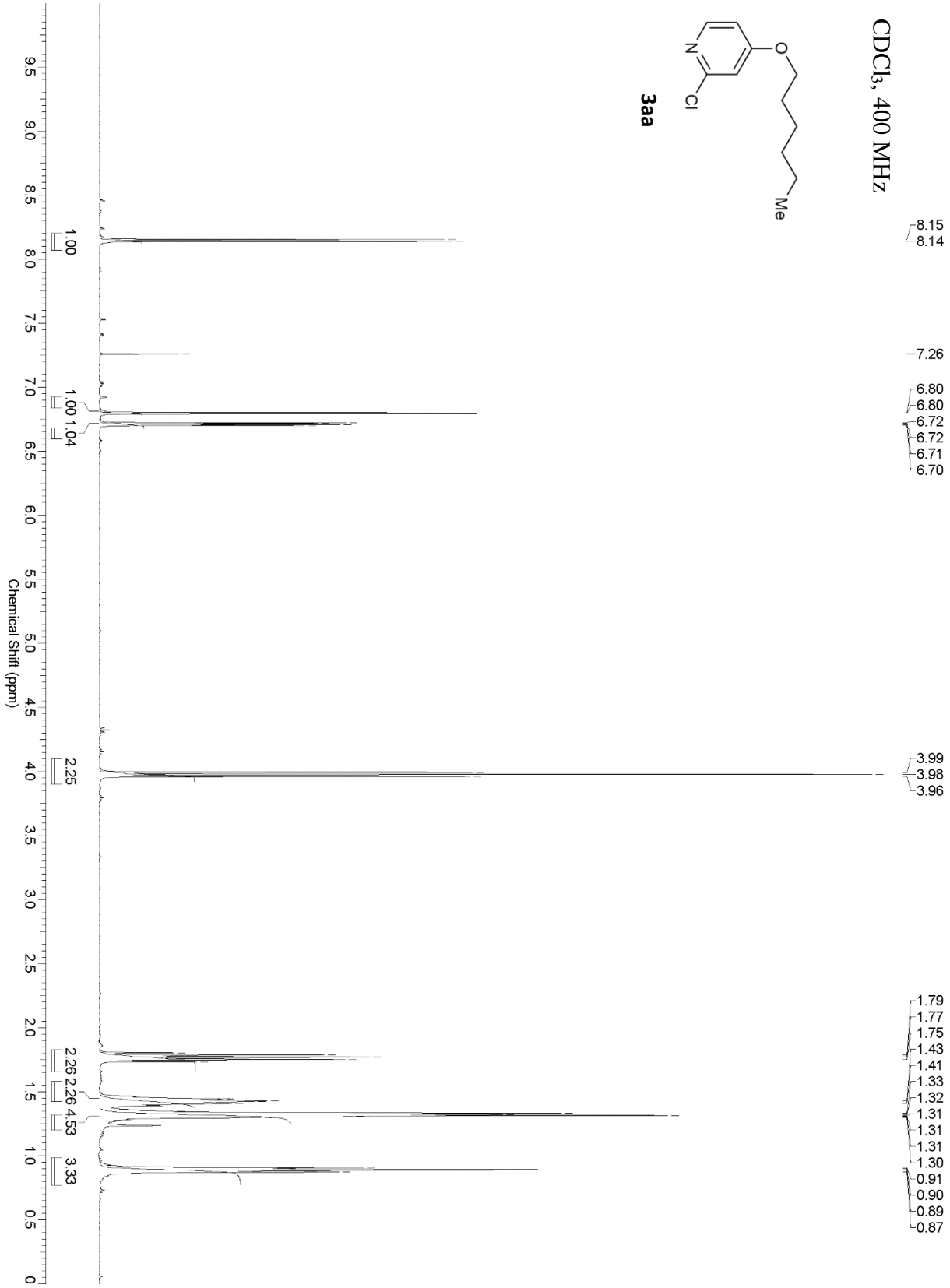

3ab
CDCl3, 100 MHz
164.53
159.07
150.78
139.34
138.31
128.87
128.71
128.56
128.23
127.04
126.82
108.99
108.02
77.32
77.00
76.78
76.68
60.06
59.77
52.56
32.05
Chemical Shift (ppm)

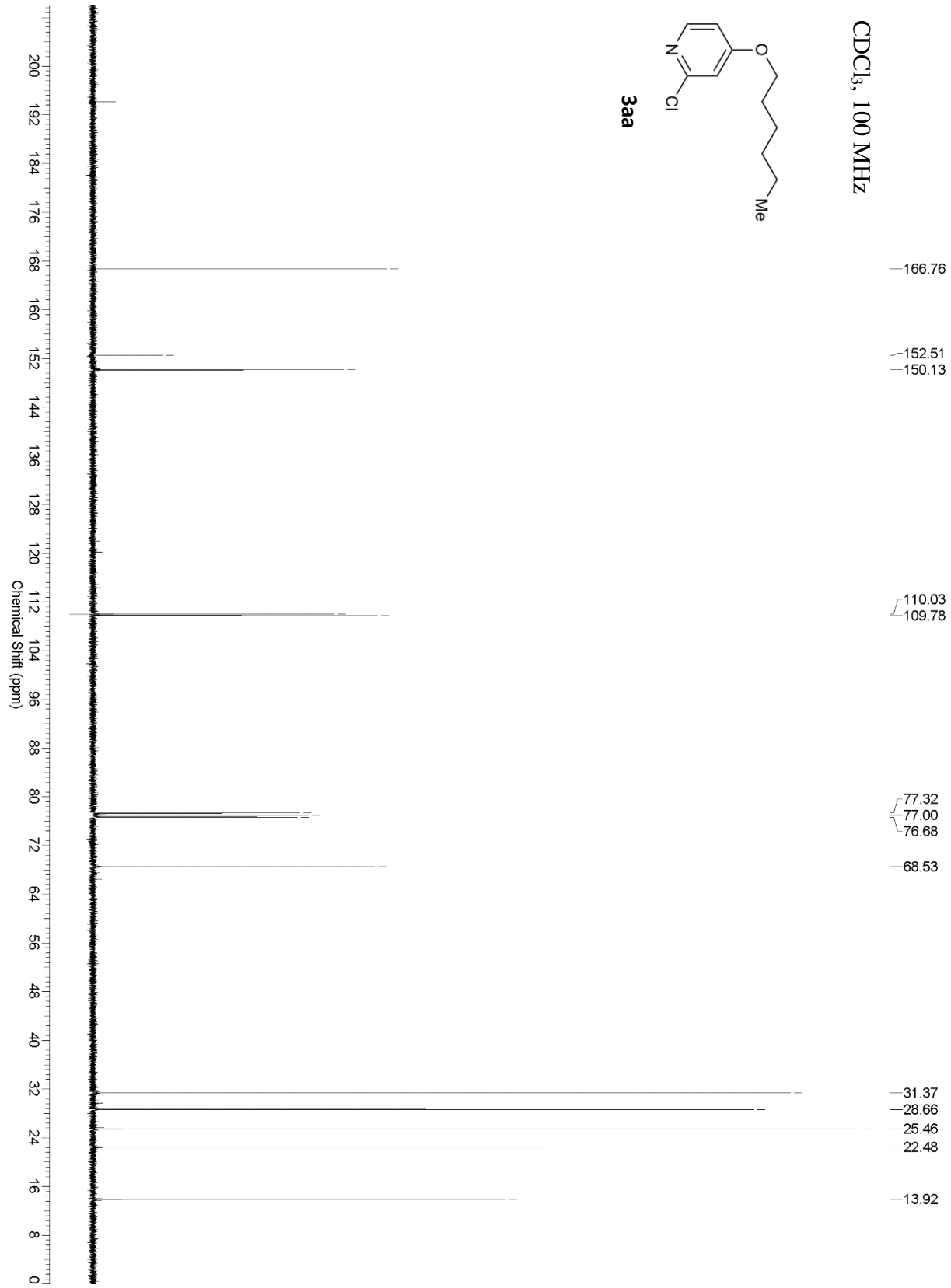

8.48
8.47
7.92
7.91
7.45
7.43
7.31
7.30
7.28
7.26
7.23
7.21
7.10
6.62
6.62
6.61
6.60
4.94
4.93
4.91
4.45
3.78
3.76
3.76
3.74
3.20
3.19
3.19
3.18
3.17
CDCl3, 400 MHz
N
O
N
3dh
1.00
2.05
7.27
4.69
2.08
1.07
1.05
1.06
1.07
2.14
2.13
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

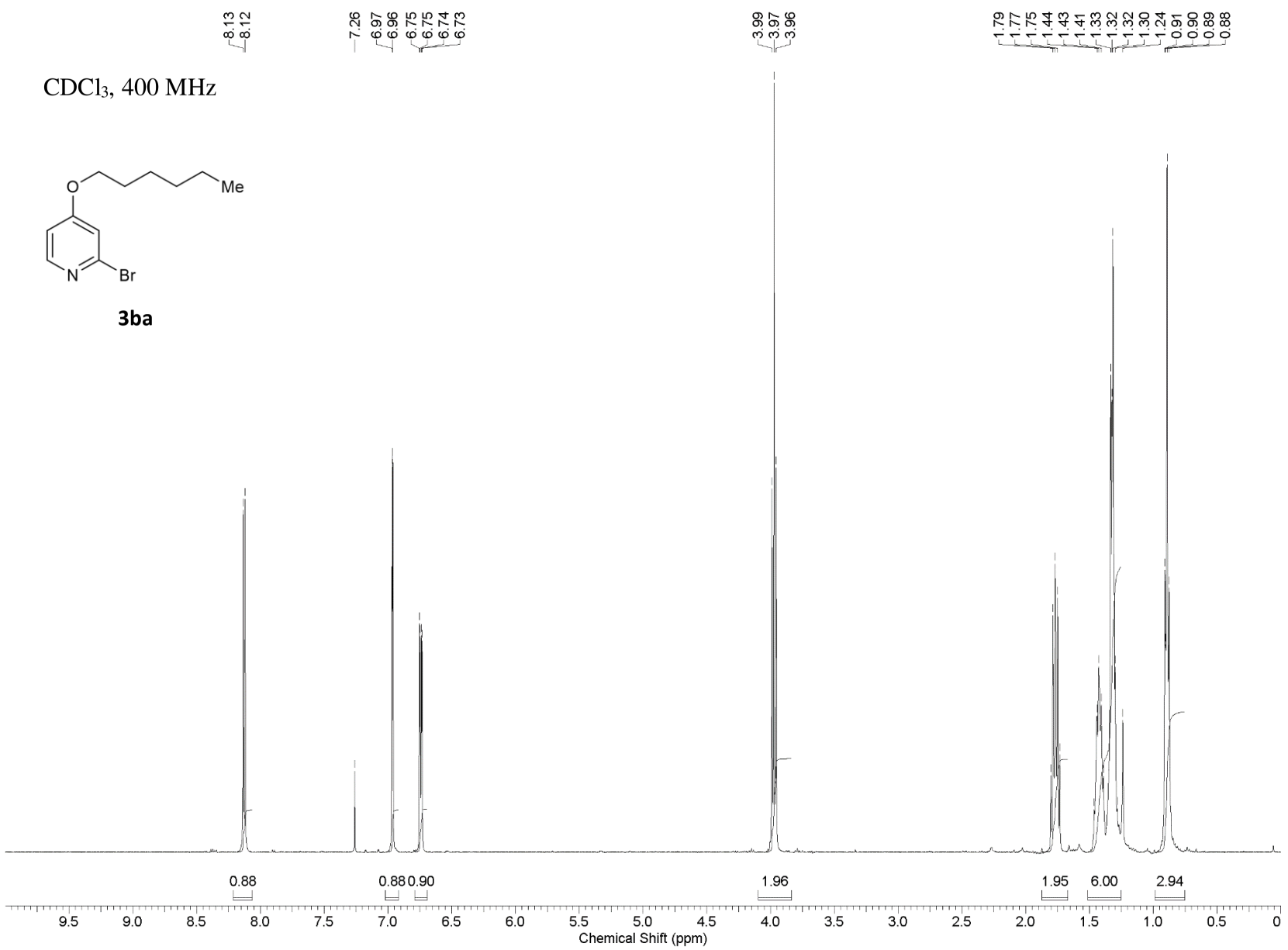

163.97
159.40
150.99
141.67
139.26
129.05
128.68
128.55
127.39
127.34
126.90
108.69
107.31
78.29
77.32
77.00
76.69
66.32
60.17
CDCl3, 100 MHz
3dh
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

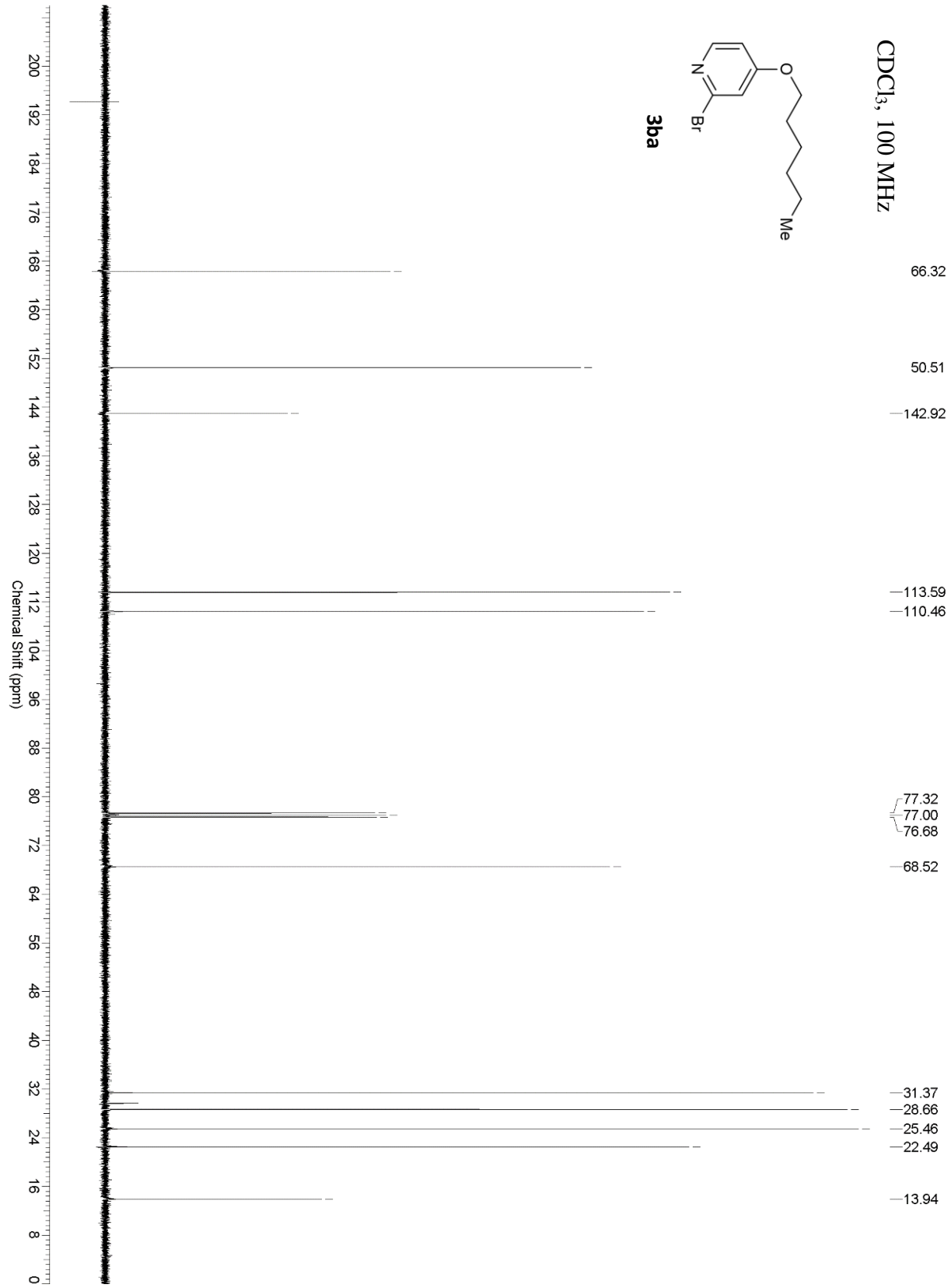

8.52
8.51
7.97
7.95
7.49
7.49
7.46
7.44
7.42
7.40
7.38
7.06
7.05
7.04
7.04
2.73
2.41
2.40
2.39
2.37
2.24
2.21
2.20
2.18
2.16
1.84
1.82
1.80
CDCl3, 400 MHz
O
N
3di
1.00
2.06
4.11
1.00
0.89
2.28
2.20
4.32
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

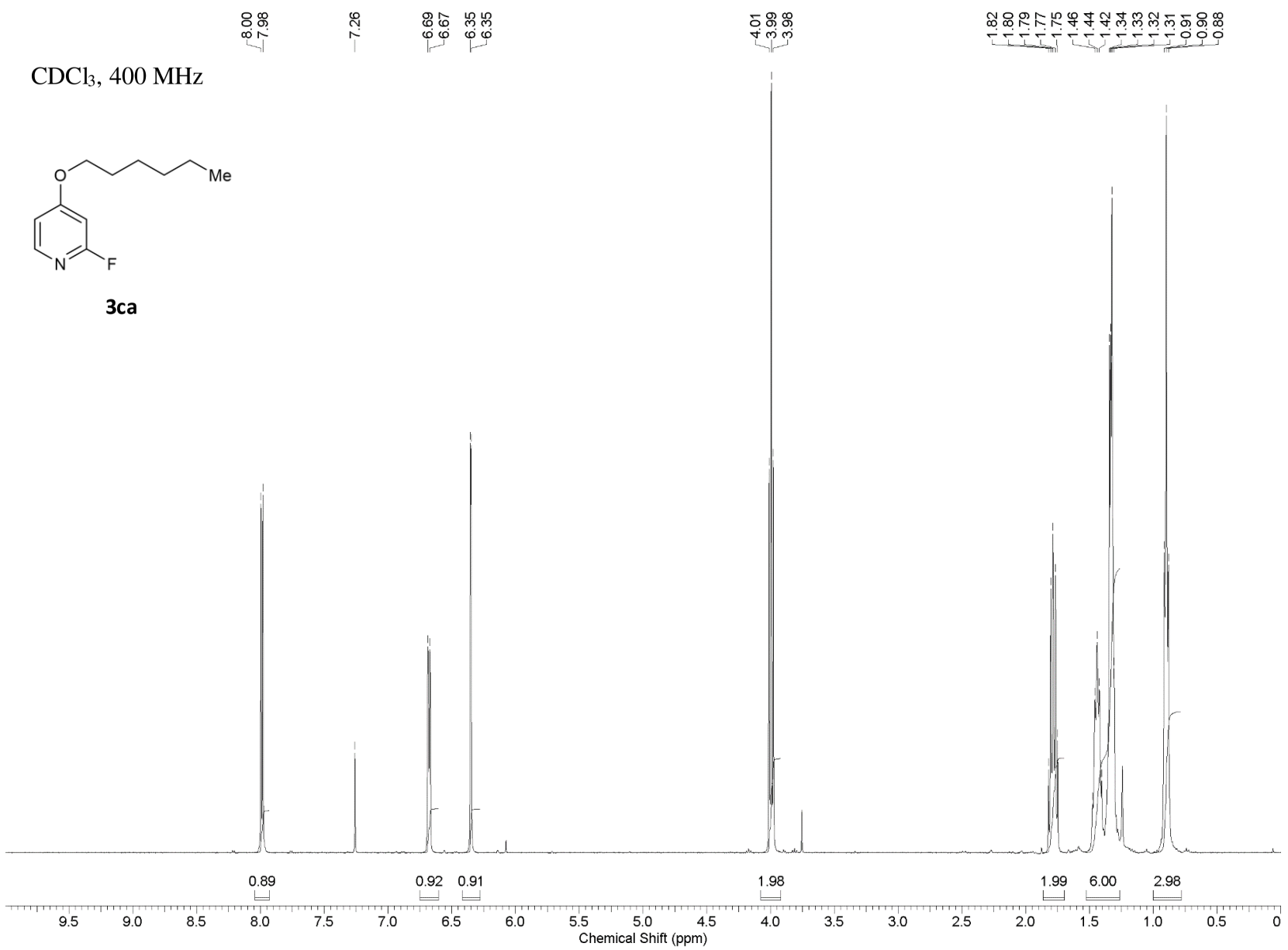

CDCl3, 100 MHz
3di
N
O
162.79
158.76
150.34
139.51
128.80
128.58
126.85
111.58
110.10
84.05
80.99
77.32
77.00
76.68
75.58
40.73
23.79
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

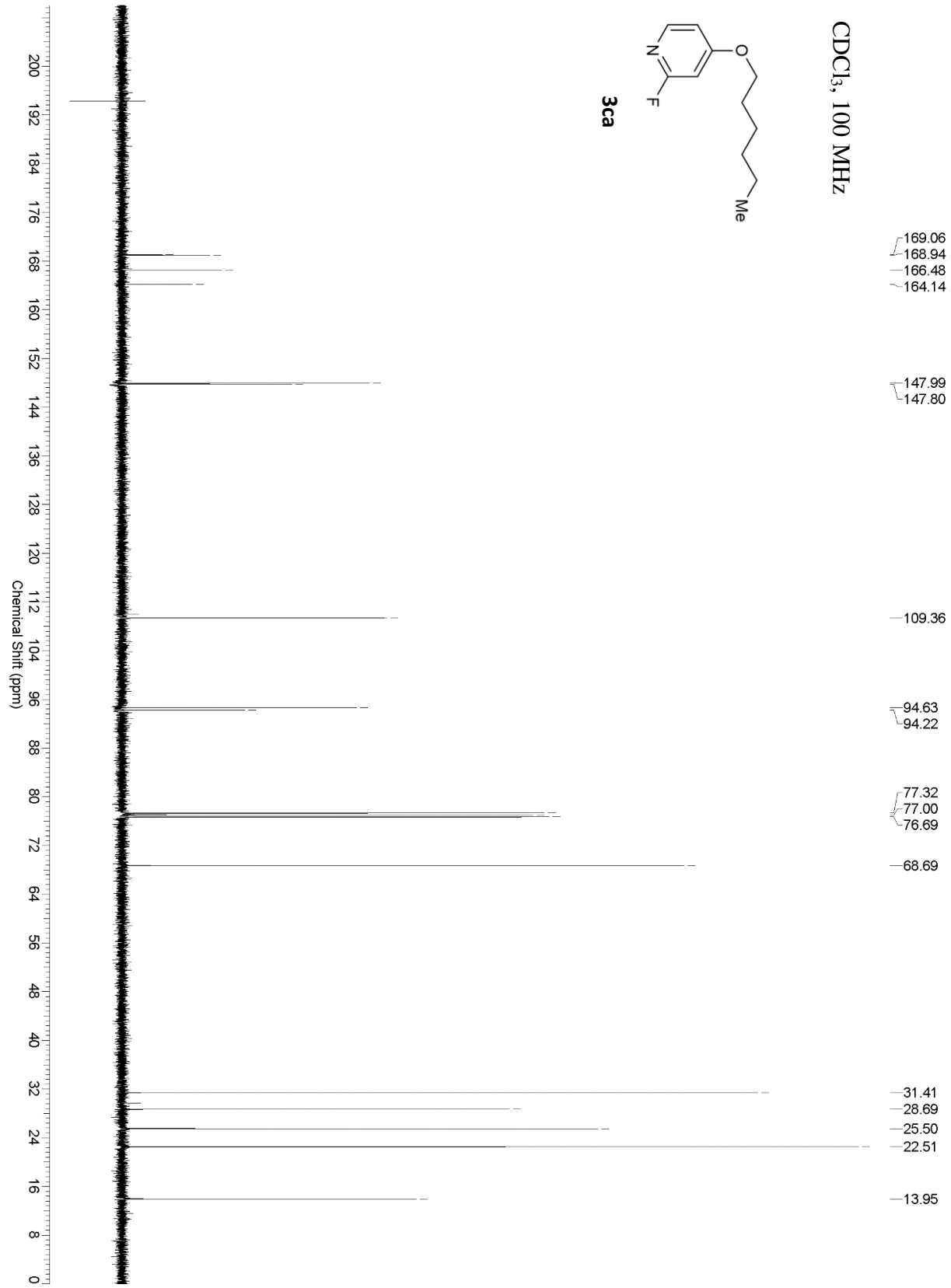

CDCl3, 400 MHz
3aa
N
Cl
O
Me
8.15
8.14
7.26
6.80
6.80
6.72
6.72
6.71
6.70
3.99
3.98
3.96
1.79
1.77
1.75
1.43
1.41
1.33
1.32
1.31
1.31
1.31
1.30
0.91
0.90
0.89
0.87
1.00
1.00
1.04
2.25
2.26
2.26
4.53
3.33
Chemical Shift (ppm)

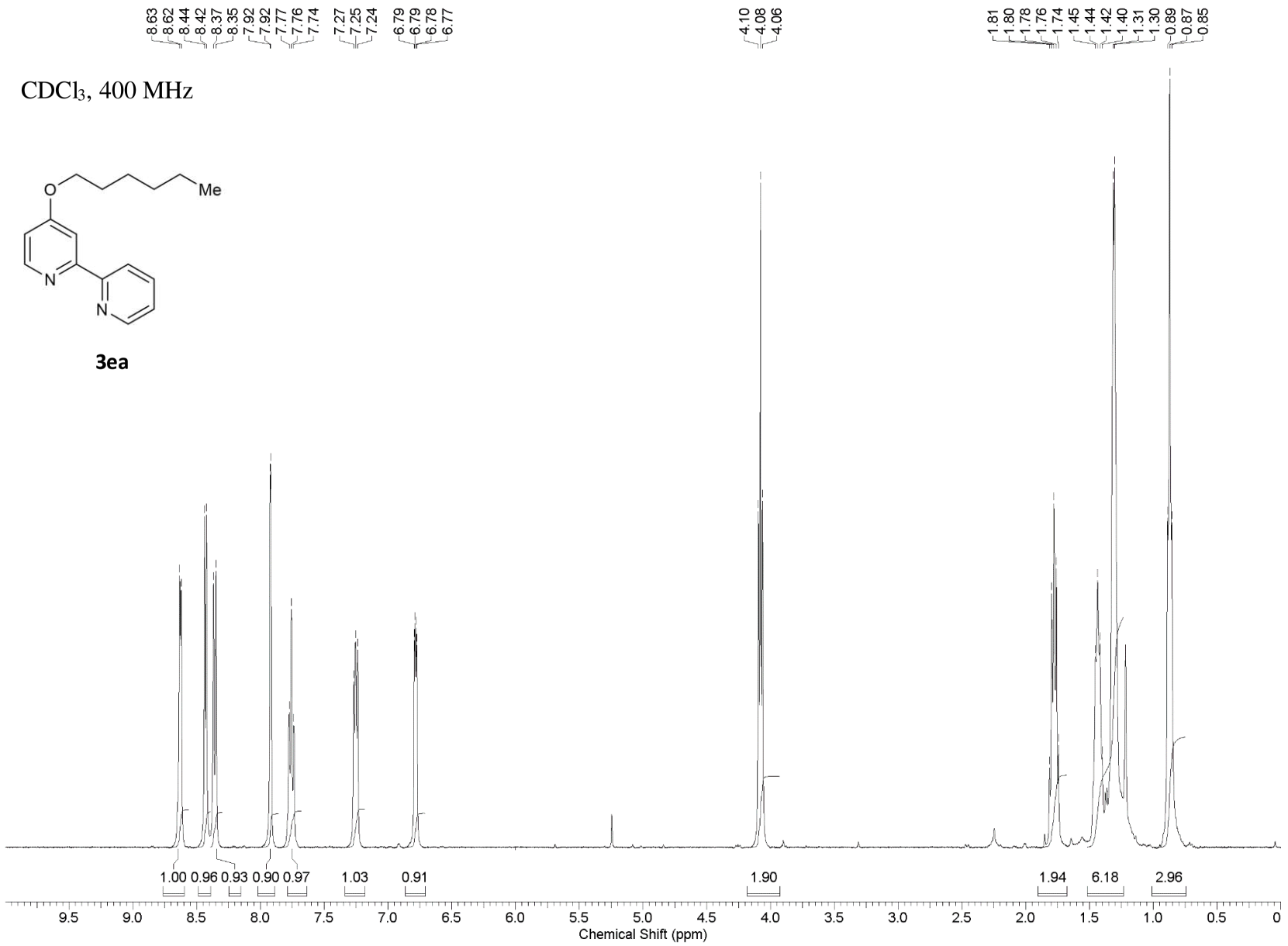

CDCl3, 100 MHz
3aa
N
Cl
O
Me
166.76
152.51
150.13
110.03
109.78
77.32
77.00
76.68
68.53
31.37
28.66
25.46
22.48
13.92
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

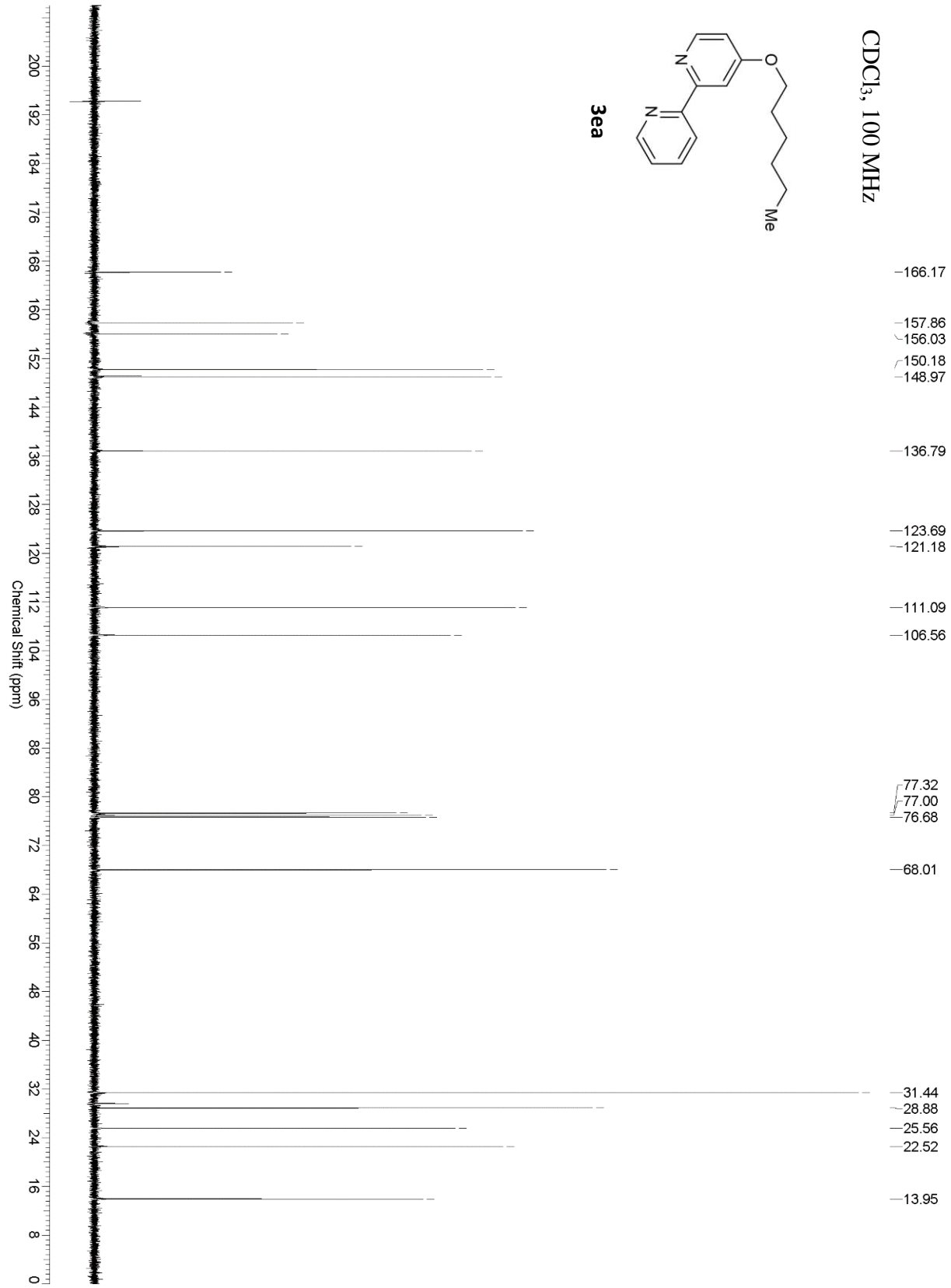

8.13
8.12
7.26
6.97
6.96
6.75
6.75
6.74
6.73
3.99
3.97
3.96
1.79
1.77
1.75
1.44
1.43
1.41
1.33
1.32
1.32
1.30
1.24
0.91
0.90
0.89
0.88
CDCl3, 400 MHz
O
Me
N
Br
3ba
0.88
0.88
0.90
1.96
1.95
6.00
2.94
Chemical Shift (ppm)

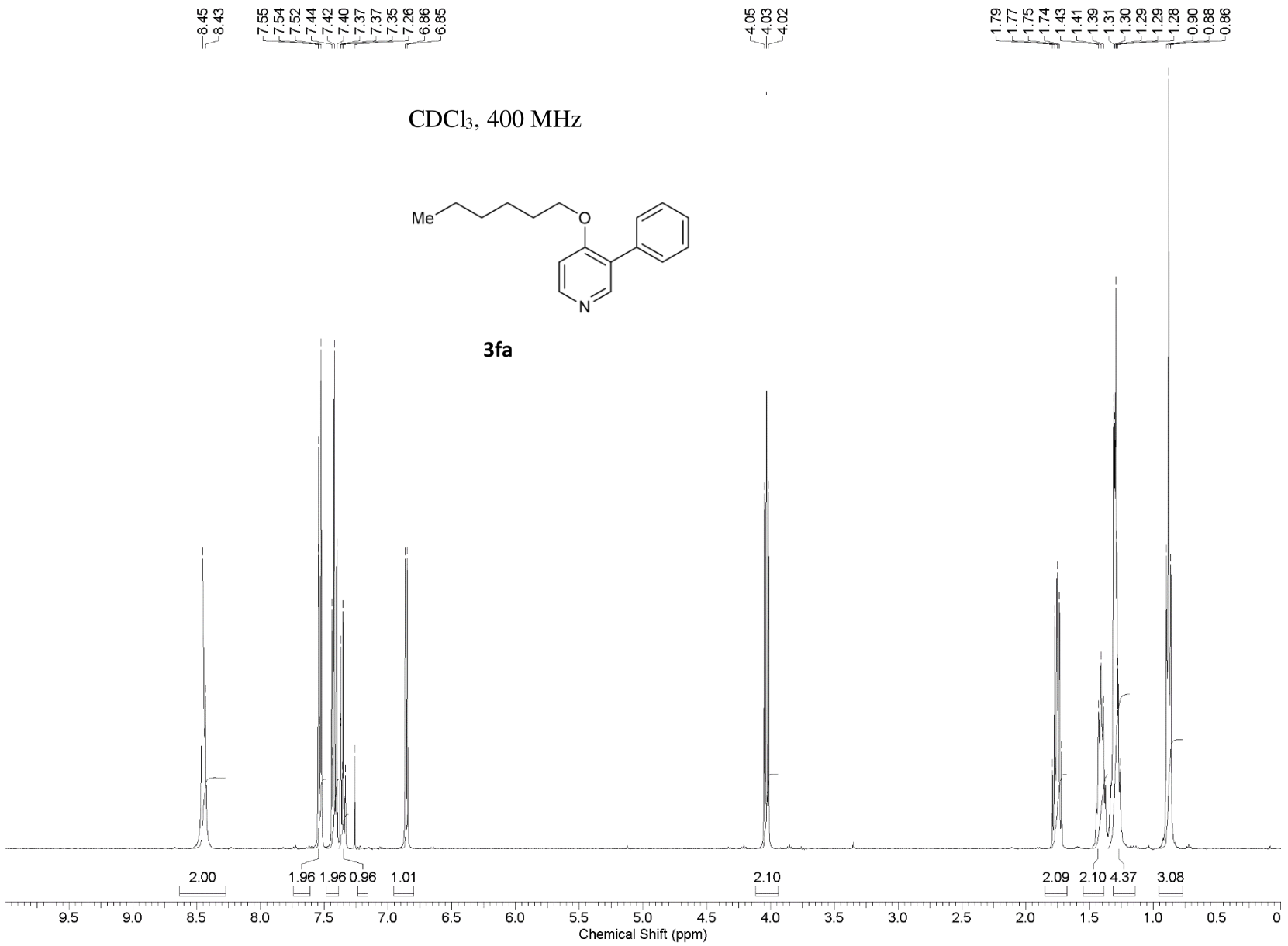

CDCl3, 100 MHz
3ba
N
Br
O
Me
66.32
50.51
142.92
113.59
110.46
77.32
77.00
76.68
68.52
31.37
28.66
25.46
22.49
13.94
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

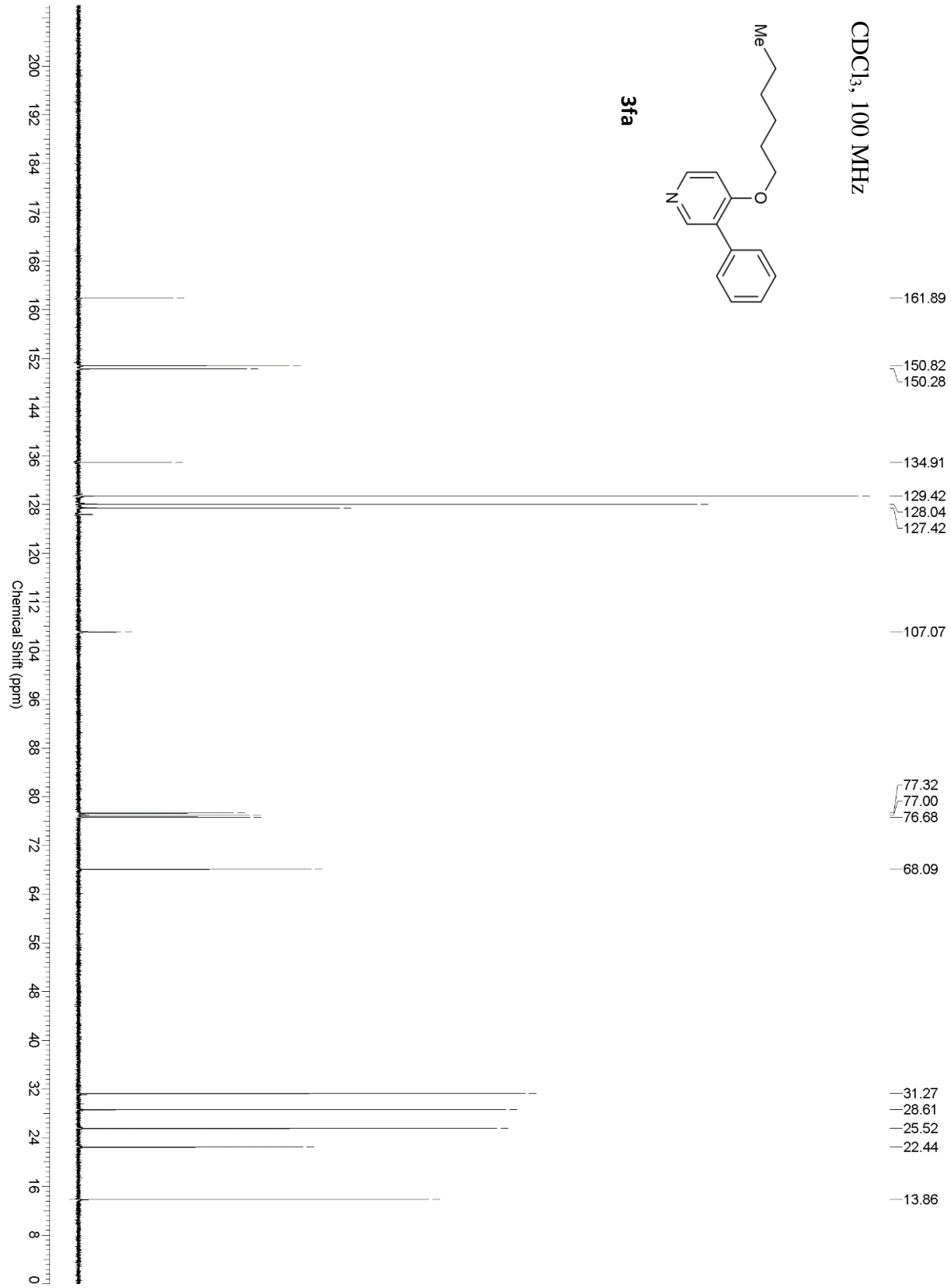

8.00
7.98
7.26
6.69
6.67
6.35
6.35
4.01
3.99
3.98
1.82
1.80
1.79
1.77
1.75
1.46
1.44
1.42
1.34
1.33
1.32
1.31
0.91
0.90
0.88
CDCl3, 400 MHz
O
Me
N
F
3ca
0.89
0.92
0.91
1.98
1.99
6.00
2.98
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

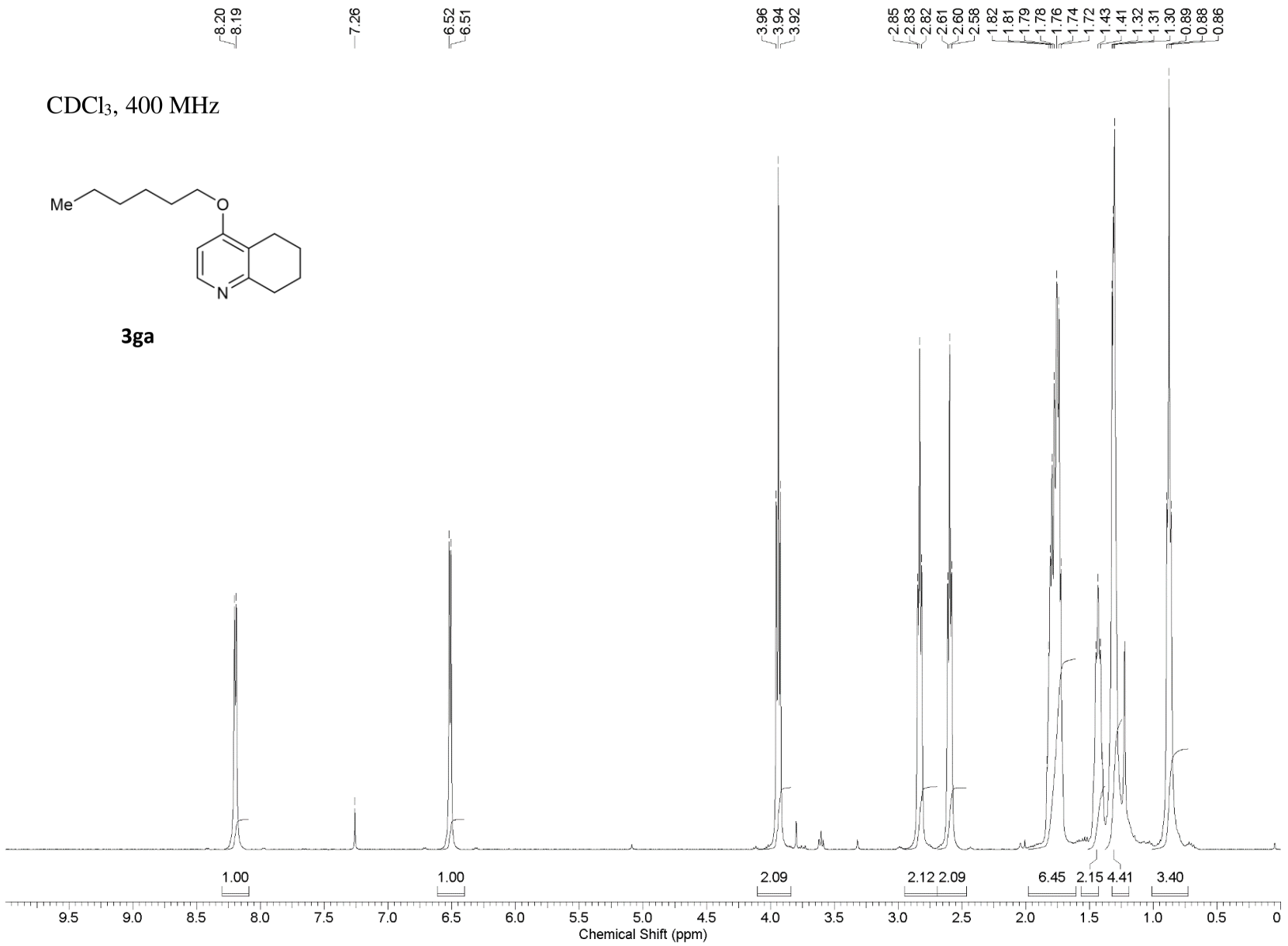

CDCl3, 100 MHz
3ca
N
F
O
Me
169.06
168.94
166.48
164.14
147.99
147.80
109.36
94.63
94.22
77.32
77.00
76.69
68.69
31.41
28.69
25.50
22.51
13.95
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

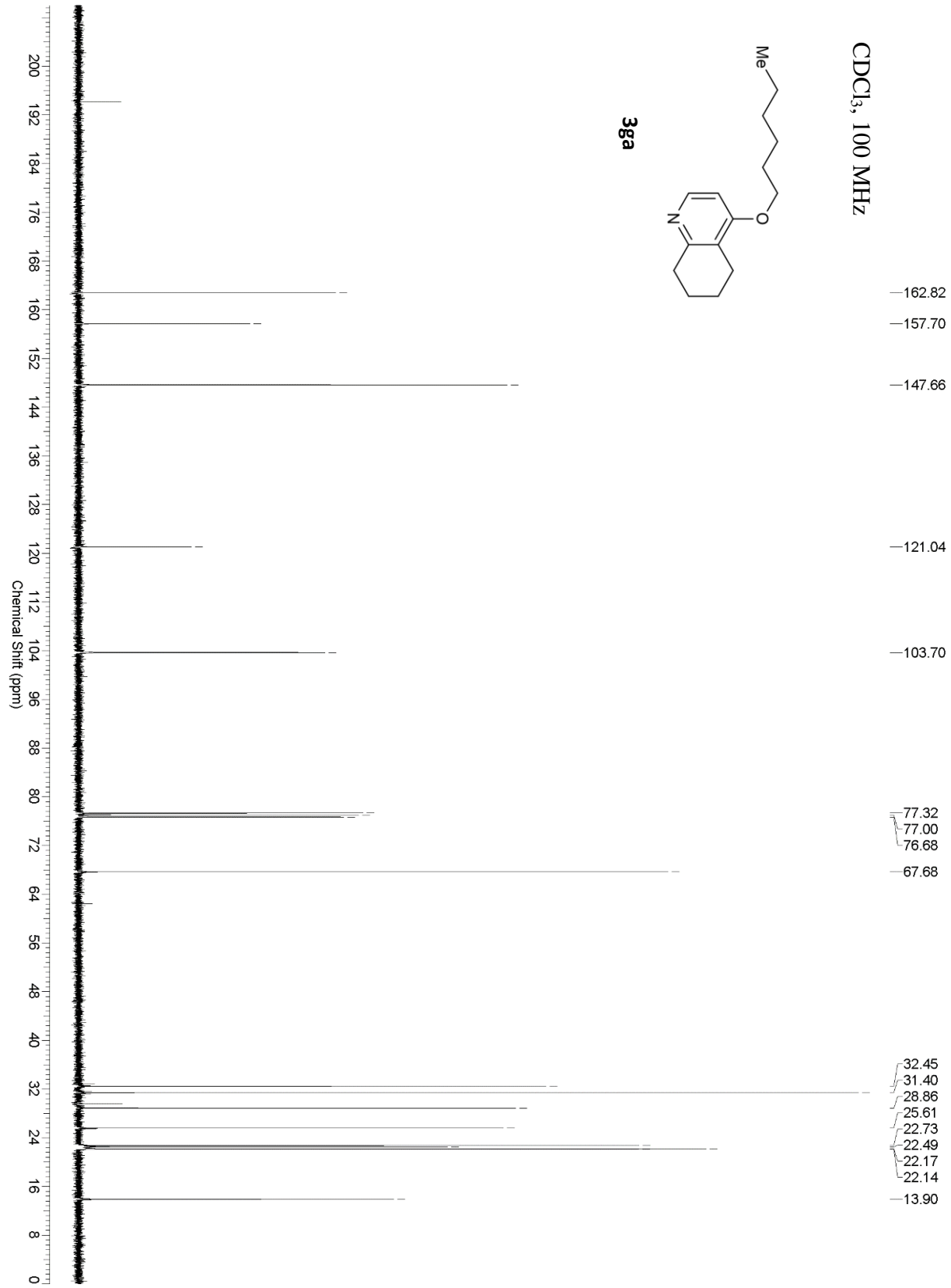

8.63
8.62
8.44
8.42
8.37
8.35
7.92
7.92
7.77
7.76
7.74
7.27
7.25
7.24
6.79
6.79
6.78
6.77
4.10
4.08
4.06
1.81
1.80
1.78
1.76
1.74
1.45
1.44
1.42
1.40
1.31
1.30
0.89
0.87
0.85
CDCl3, 400 MHz
O
Me
N
N
3ea
1.00 0.96 0.93 0.90 0.97 1.03 0.91 1.90 1.94 6.18 2.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

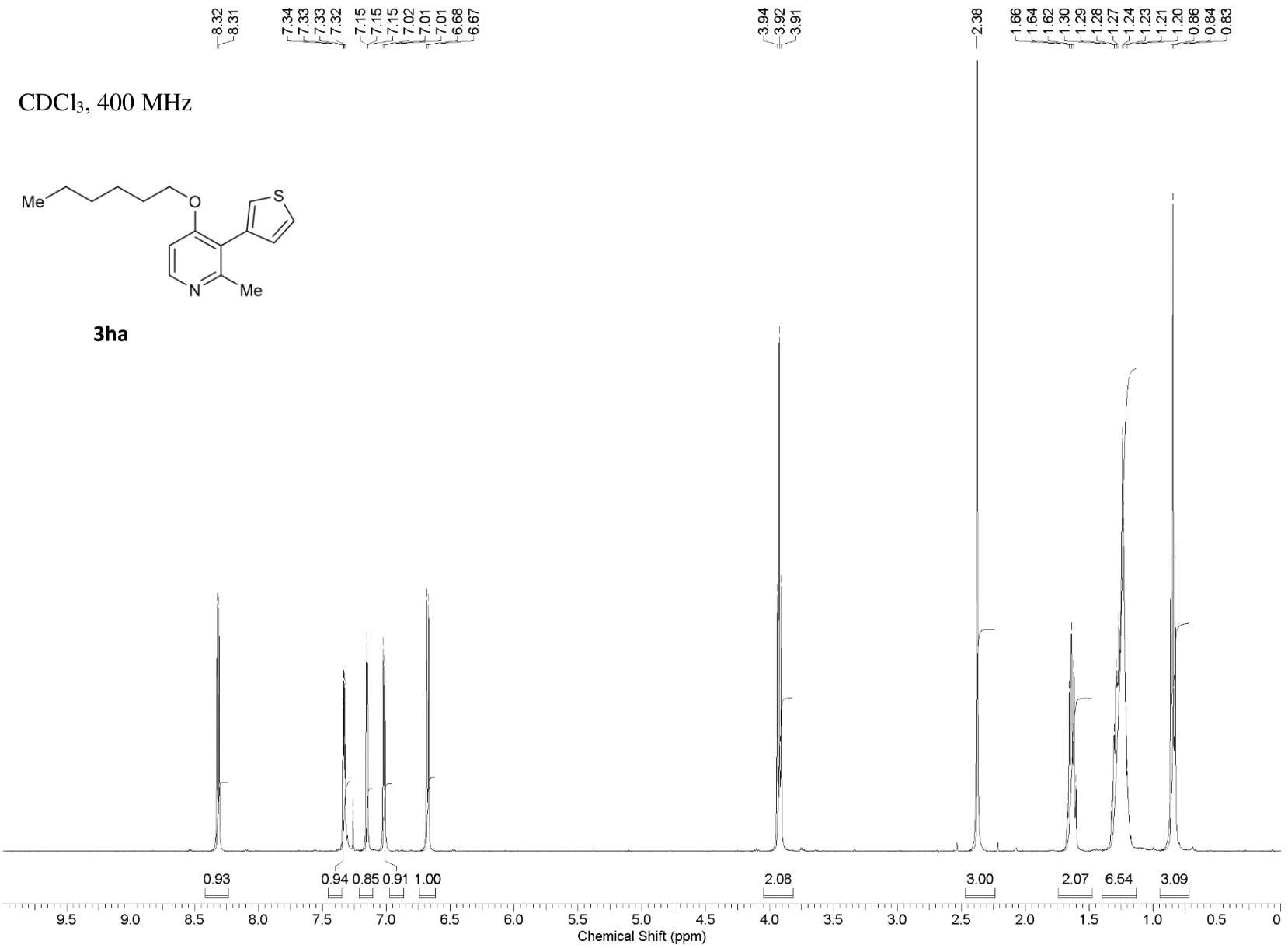

CDCl3, 100 MHz
3ea
N
N
O
Me
166.17
157.86
156.03
150.18
148.97
136.79
123.69
121.18
111.09
106.56
77.32
77.00
76.68
68.01
31.44
28.88
25.56
22.52
13.95
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

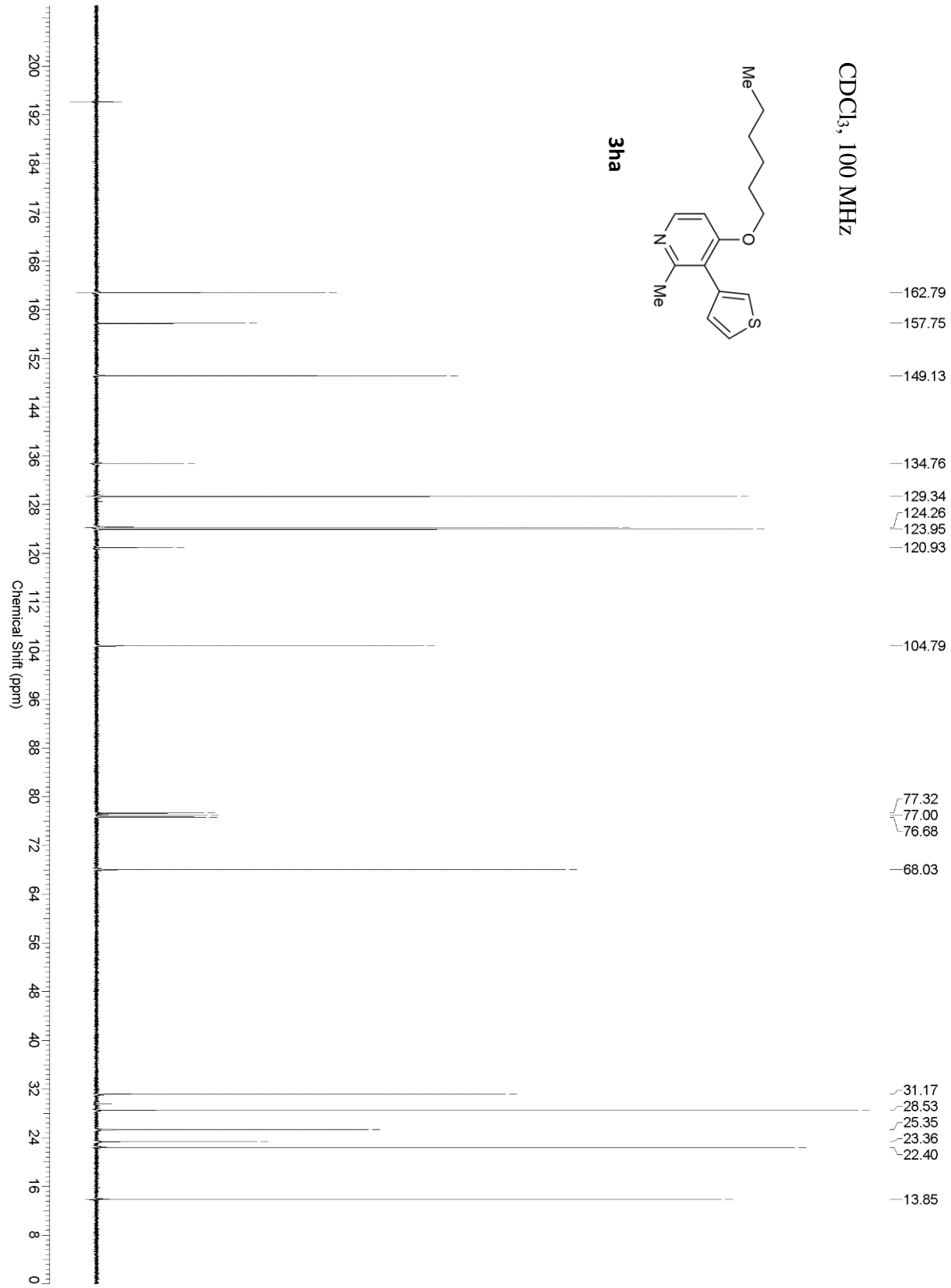

8.45
8.43
7.55
7.54
7.52
7.44
7.42
7.40
7.37
7.37
7.35
7.26
6.86
6.85
4.05
4.03
4.02
1.79
1.77
1.75
1.74
1.43
1.41
1.39
1.31
1.30
1.29
1.29
1.28
0.90
0.88
0.86
CDCl3, 400 MHz
Me
O
N
3fa
2.00
1.96
1.96
0.96
1.01
2.10
2.09
2.10
4.37
3.08
Chemical Shift (ppm)


CDCl3, 100 MHz
3fa
Me
O
N
161.89
150.82
150.28
134.91
129.42
128.04
127.42
107.07
77.32
77.00
76.68
68.09
31.27
28.61
25.52
22.44
13.86
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

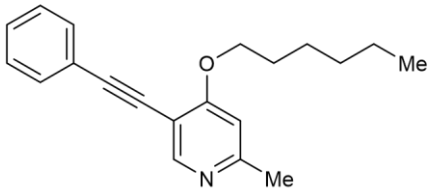

8.20
8.19
7.26
6.52
6.51
3.96
3.94
3.92
2.85
2.83
2.82
2.61
2.60
2.58
1.82
1.81
1.79
1.78
1.76
1.74
1.72
1.43
1.41
1.32
1.31
1.30
0.89
0.88
0.86
CDCl3, 400 MHz
Me
O
N
3ga
1.00
1.00
2.09
2.12 2.09
6.45
2.15
4.41
3.40
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


CDCl3, 100 MHz
3ga
Me
N
O
162.82
157.70
147.66
121.04
103.70
77.32
77.00
76.68
67.68
32.45
31.40
28.86
25.61
22.73
22.49
22.17
22.14
13.90
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

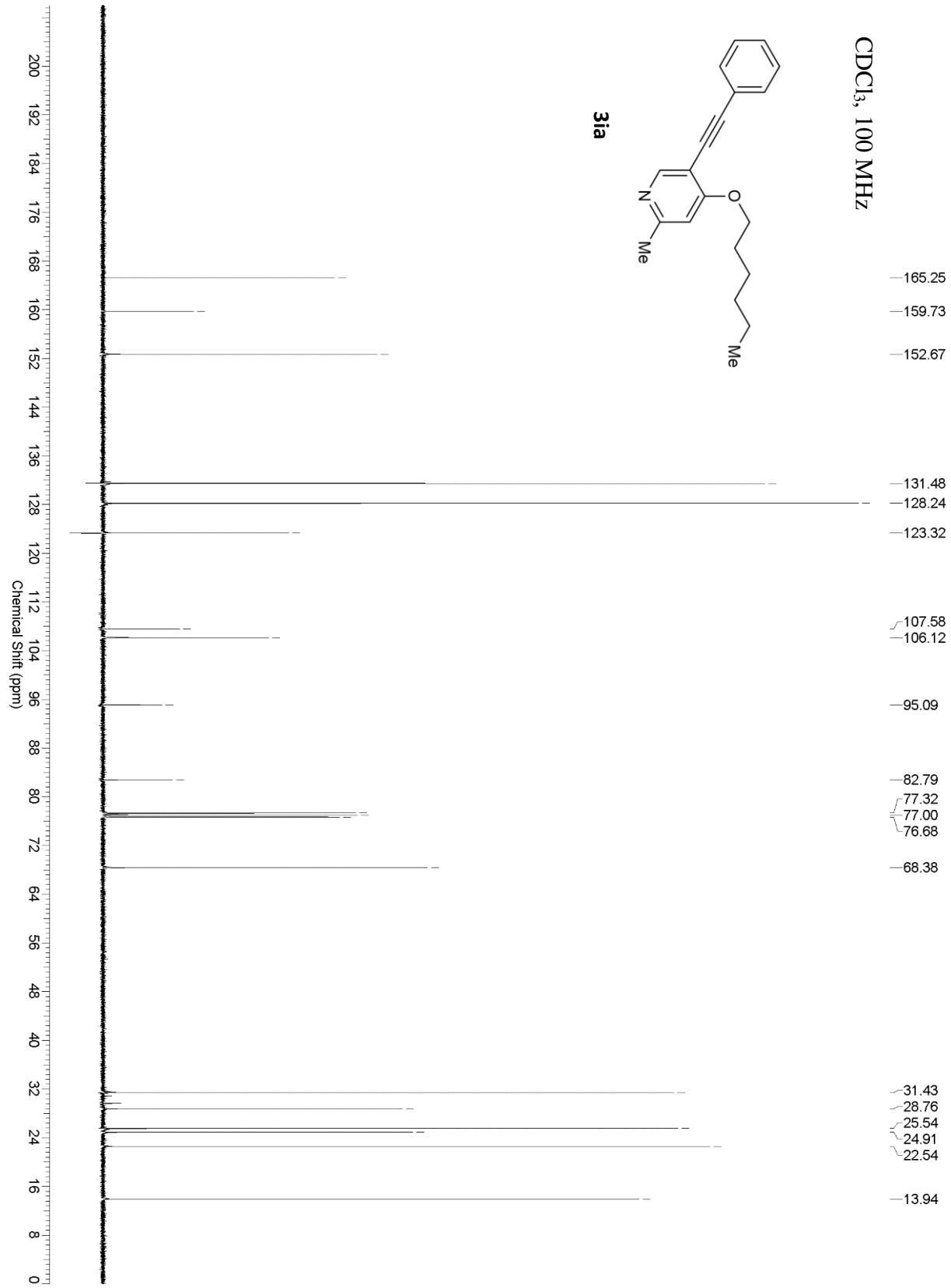

8.32
8.31
7.34
7.33
7.33
7.32
7.15
7.15
7.15
7.02
7.01
7.01
6.68
6.67
3.94
3.92
3.91
2.38
1.66
1.64
1.62
1.30
1.29
1.28
1.27
1.24
1.23
1.21
1.20
0.86
0.84
0.83
CDCl3, 400 MHz
Me
O
S
N
Me
3ha
0.93
0.94
0.85
0.91
1.00
2.08
3.00
2.07
6.54
3.09
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

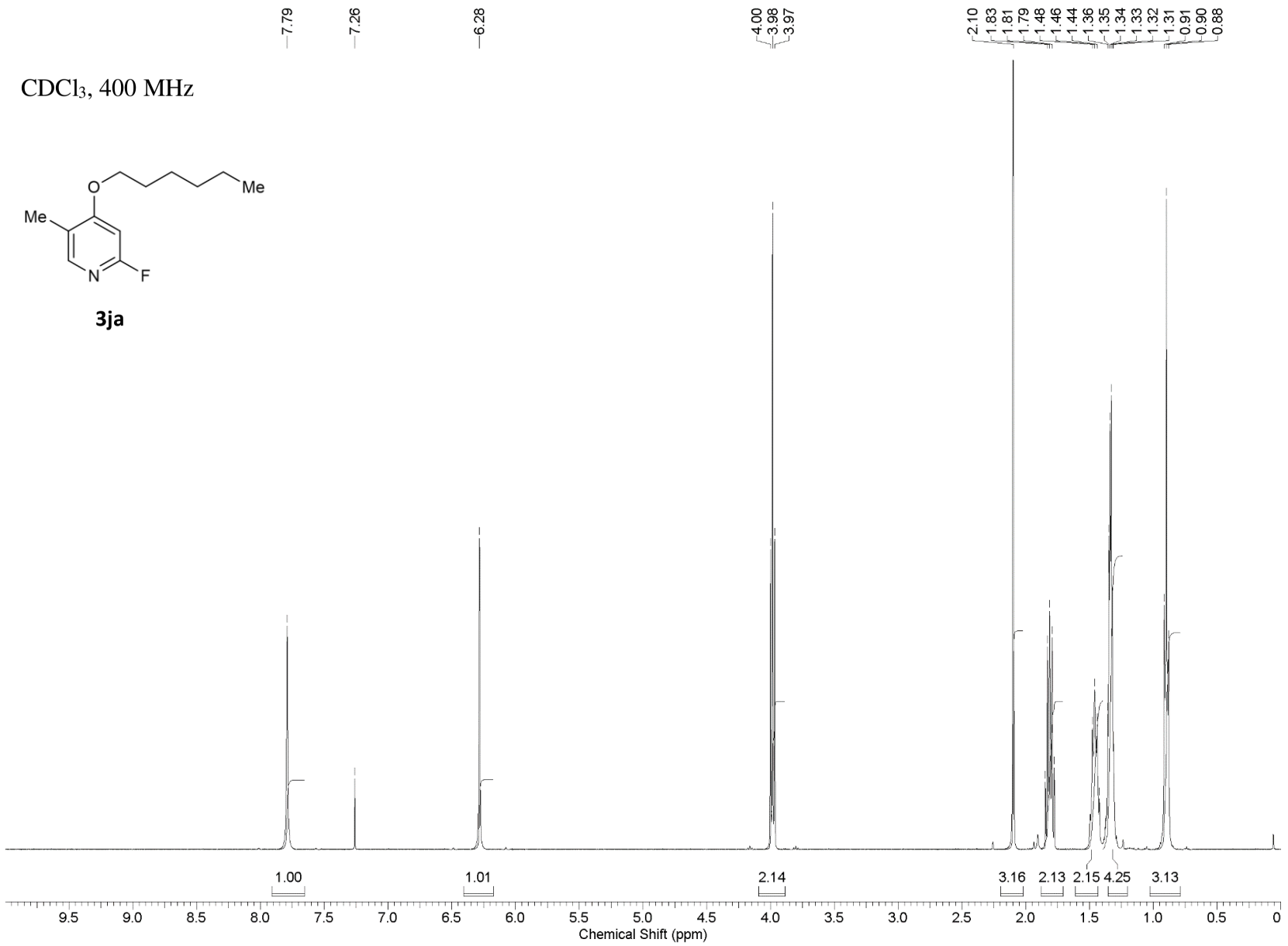

CDCl3, 100 MHz
3ha
Me
O
N
Me
S
162.79
157.75
149.13
134.76
129.34
124.26
123.95
120.93
104.79
77.32
77.00
76.68
68.03
31.17
28.53
25.35
23.36
22.40
13.85
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

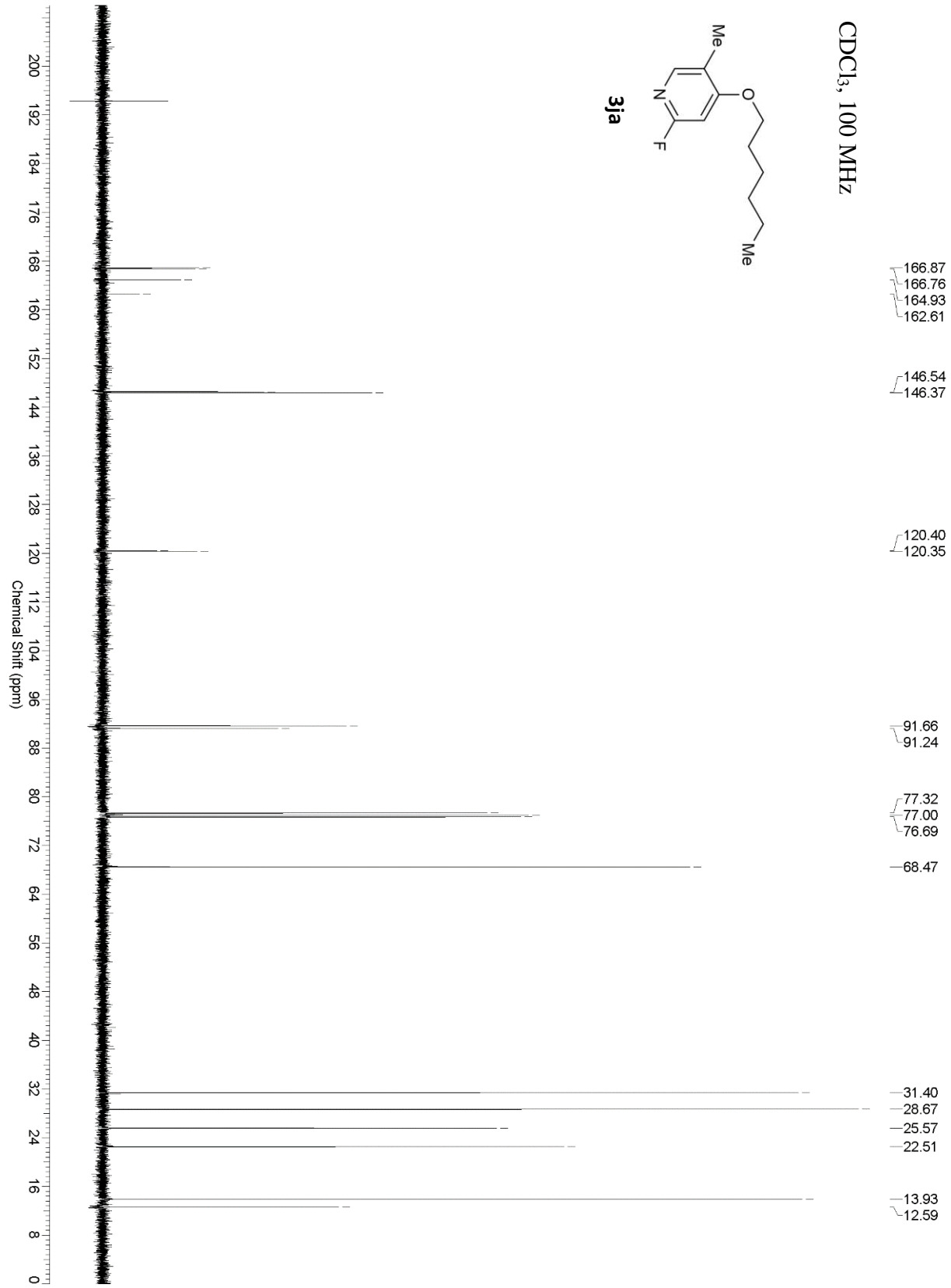
$CDCl_3$, 400 MHz



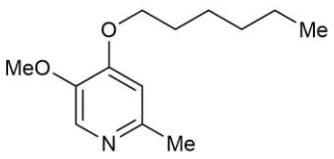
3ia


CDCl3, 100 MHz
3ia
N
Me
O
Me
165.25
159.73
152.67
131.48
128.24
123.32
107.58
106.12
95.09
82.79
77.32
77.00
76.68
68.38
31.43
28.76
25.54
24.91
22.54
13.94
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

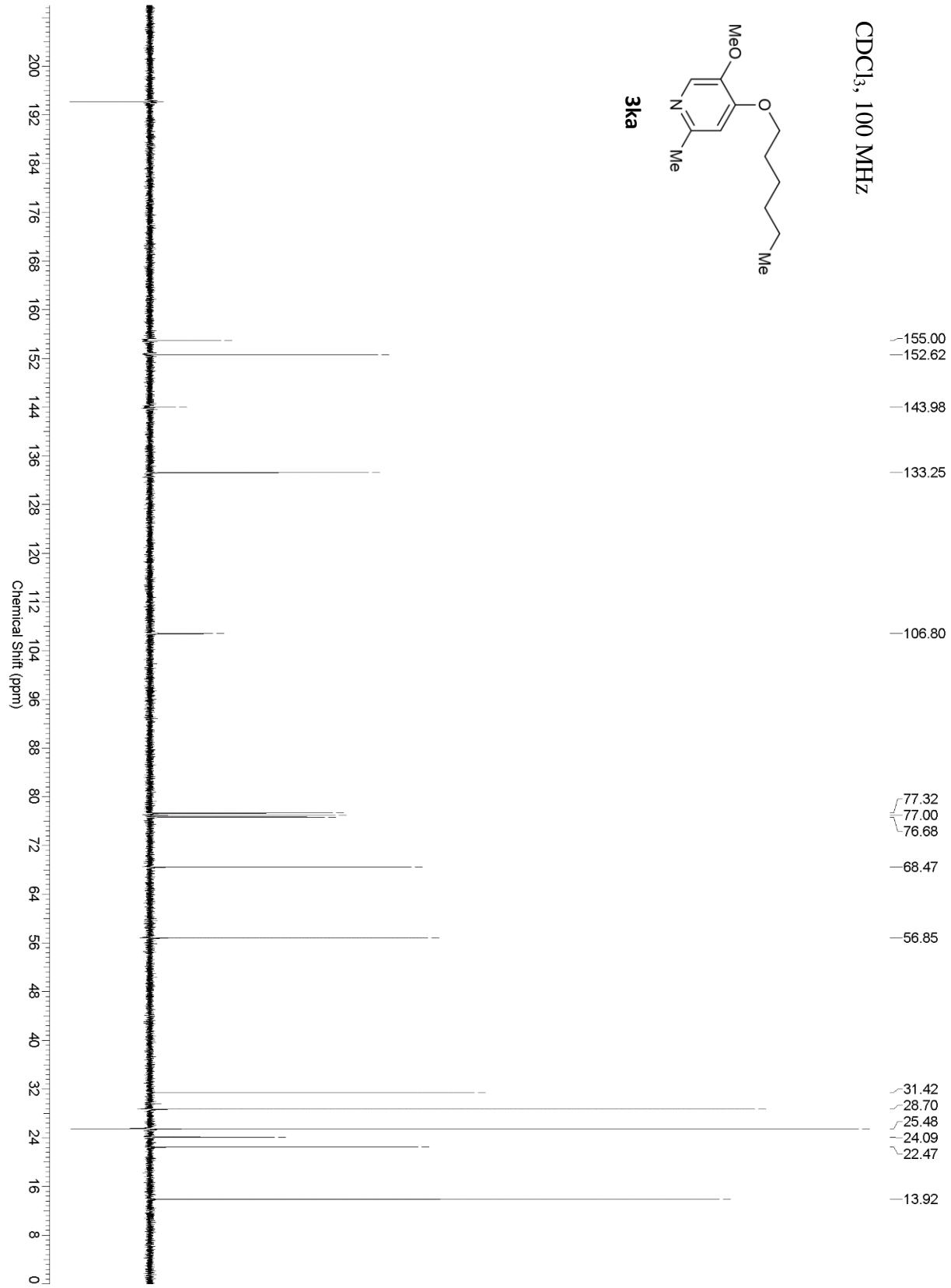

7.79
7.26
6.28
4.00
3.98
3.97
2.10
1.83
1.81
1.79
1.48
1.46
1.44
1.36
1.35
1.34
1.33
1.32
1.31
0.91
0.90
0.88
CDCl3, 400 MHz
O
Me
Me
N
F
3ja
1.00
1.01
2.14
3.16
2.13
2.15
4.25
3.13
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

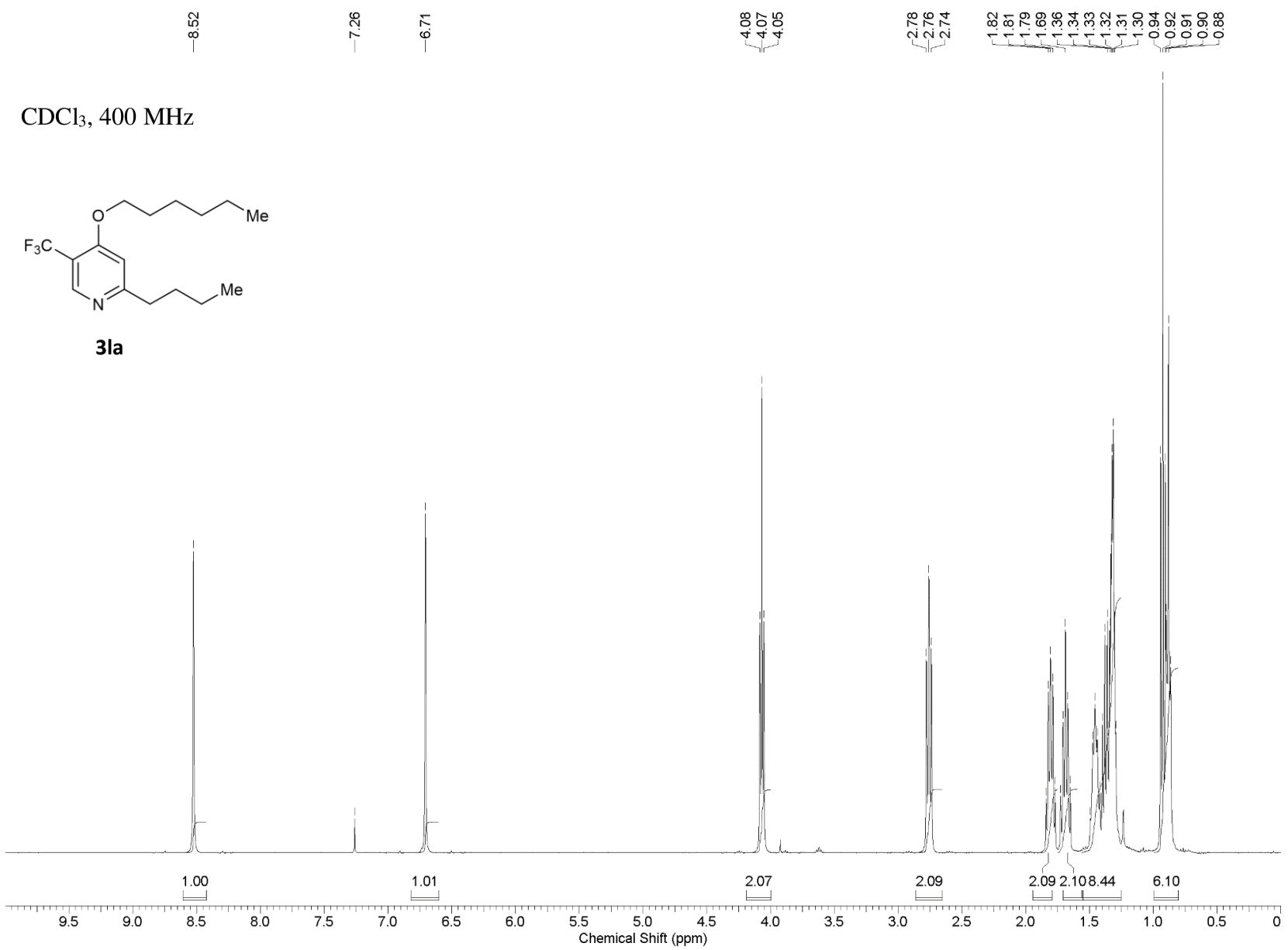

CDCl3, 100 MHz
3ja
Me
N
O
F
Me
166.87
166.76
164.93
162.61
146.54
146.37
120.40
120.35
91.66
91.24
77.32
77.00
76.69
68.47
31.40
28.67
25.57
22.51
13.93
12.59
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

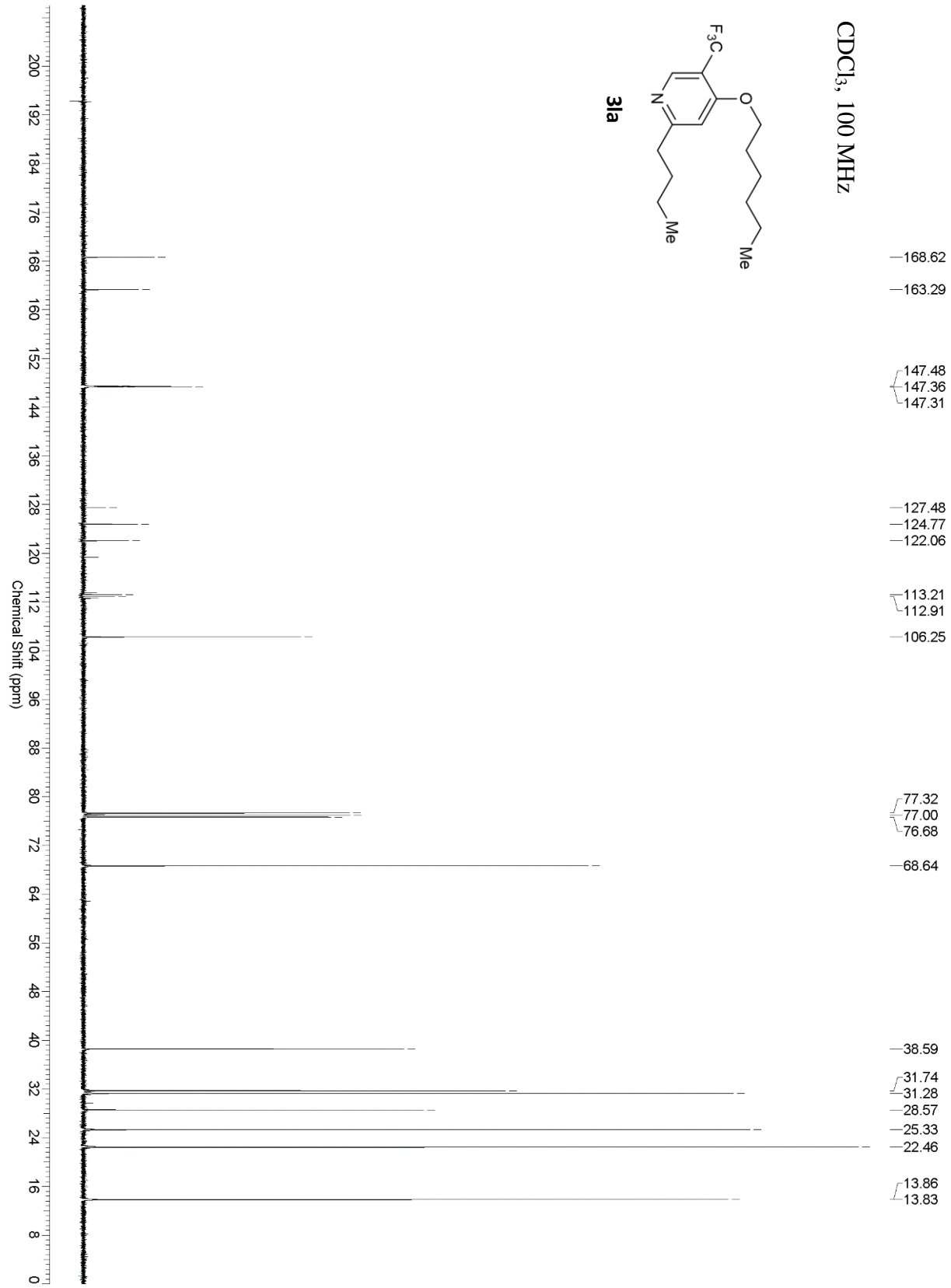
$CDCl_3$, 400 MHz

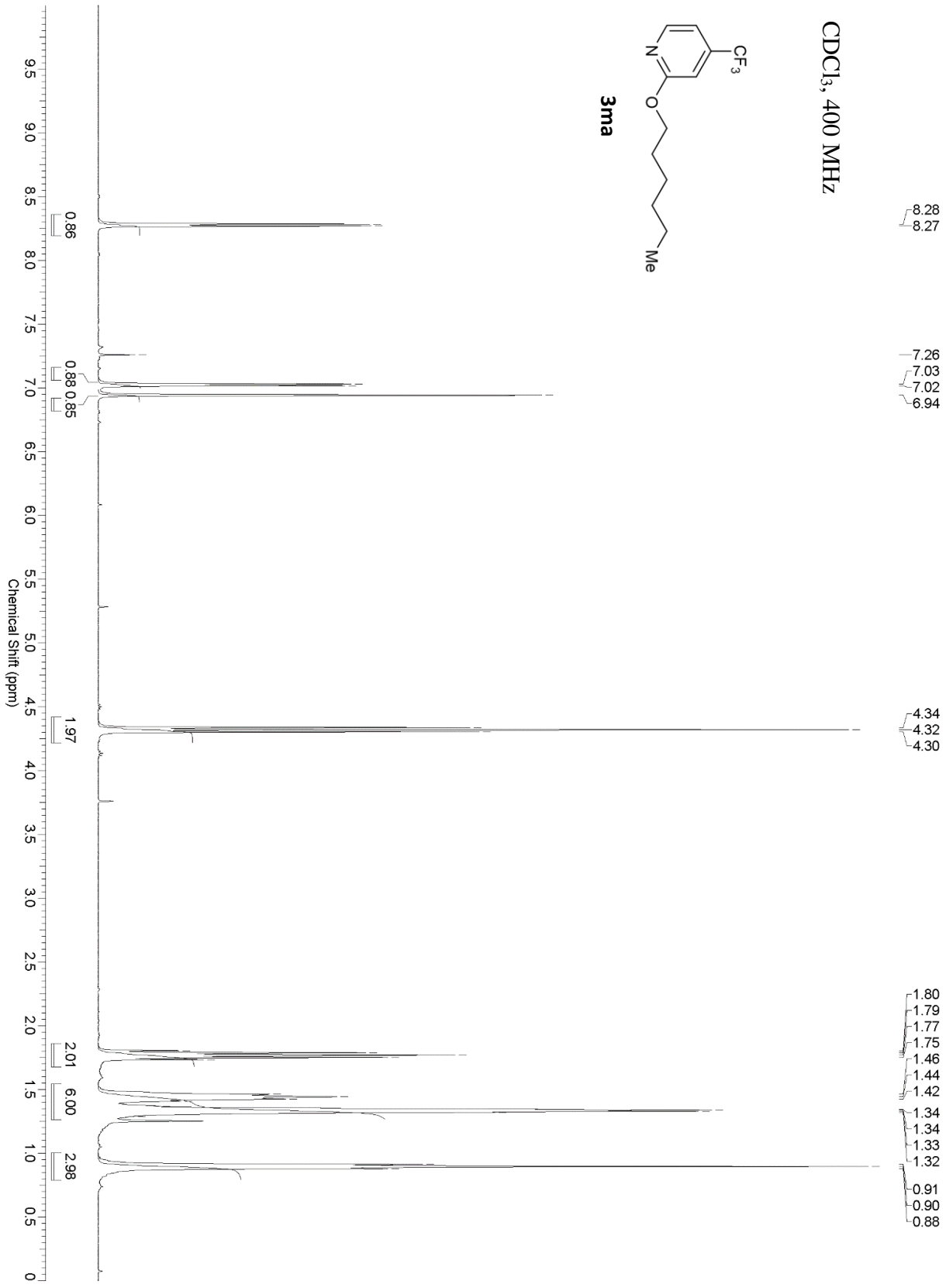


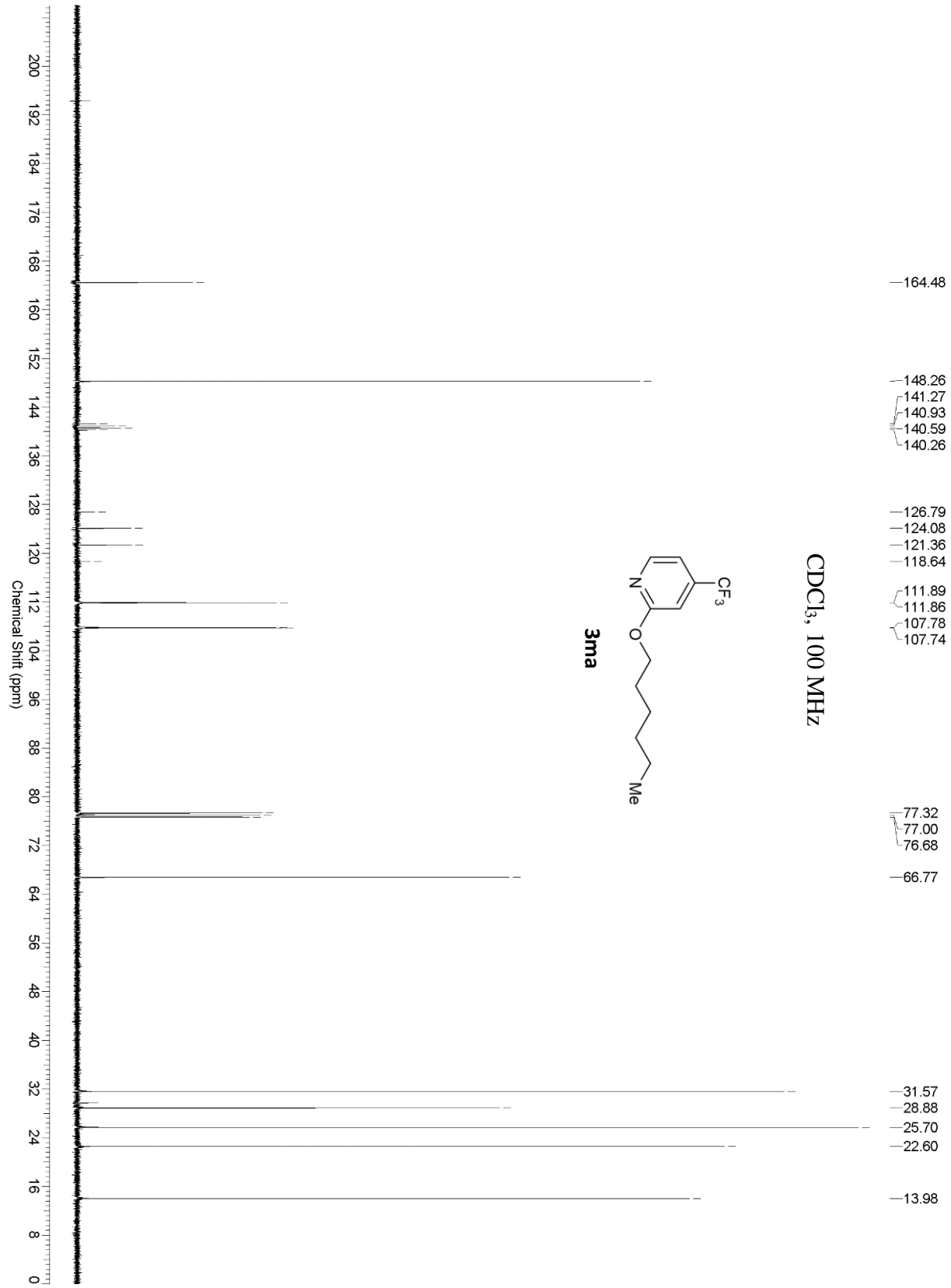
3ka

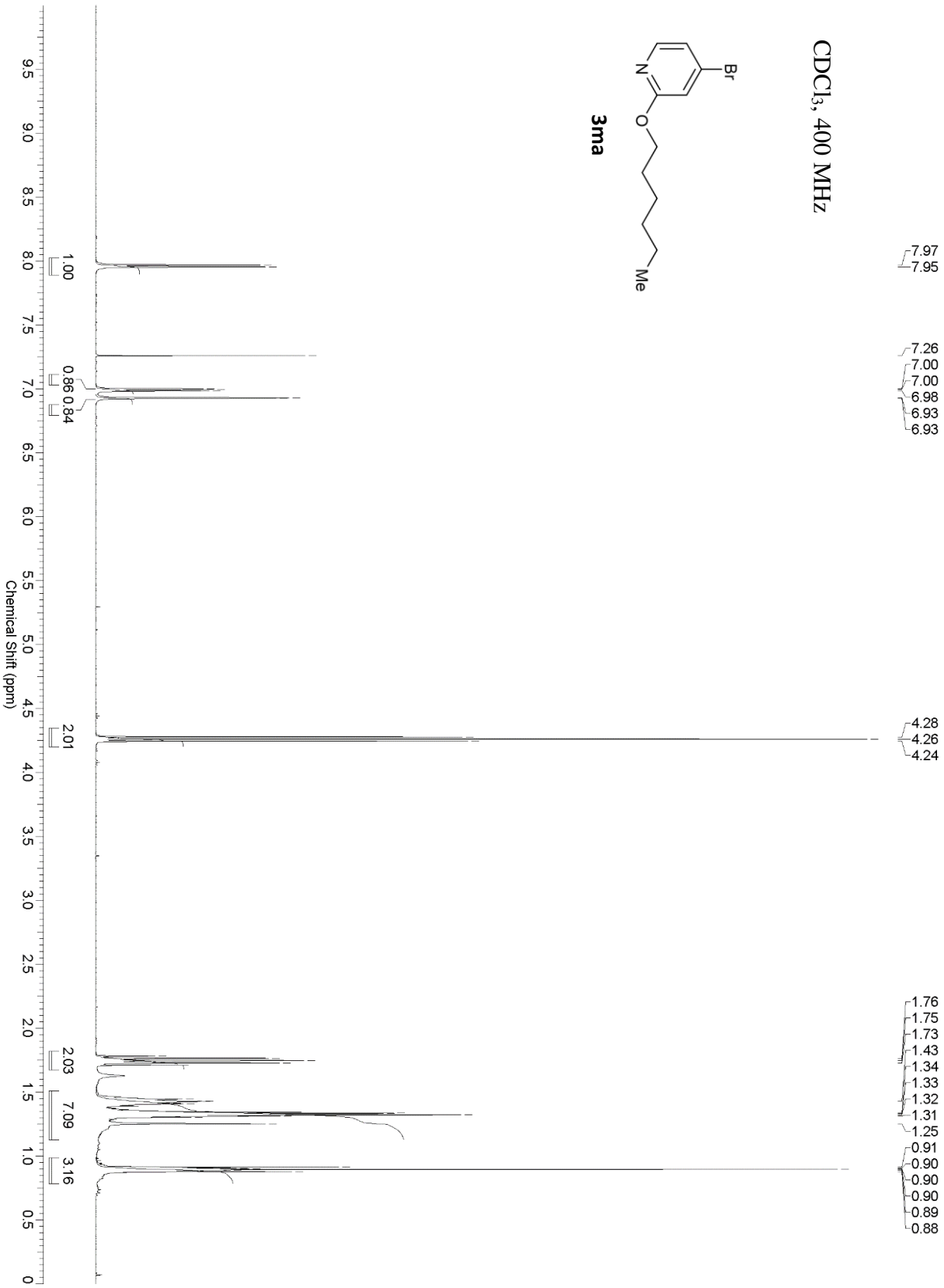

CDCl3, 100 MHz
3ka
MeO
N
Me
O
Me
155.00
152.62
143.98
133.25
106.80
77.32
77.00
76.68
68.47
56.85
31.42
28.70
25.48
24.09
22.47
13.92
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0


8.52
7.26
6.71
4.08
4.07
4.05
2.78
2.76
2.74
1.82
1.81
1.79
1.69
1.36
1.34
1.33
1.32
1.31
1.30
0.94
0.92
0.91
0.90
0.88
CDCl3, 400 MHz
O
Me
F3C
N
Me
3la
1.00
1.01
2.07
2.09
2.09
2.10
8.44
6.10
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

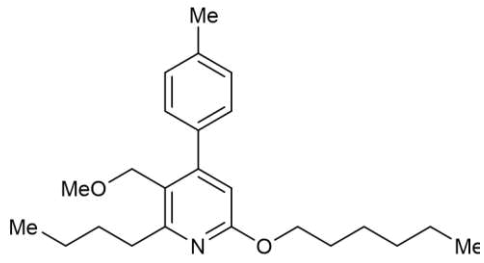

CDCl3, 100 MHz
3la
F3C
N
O
Me
Me
168.62
163.29
147.48
147.36
147.31
127.48
124.77
122.06
113.21
112.91
106.25
77.32
77.00
76.68
68.64
38.59
31.74
31.28
28.57
25.33
22.46
13.86
13.83
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0


CDCl3, 400 MHz
3ma
CF3
N
O
Me
8.28
8.27
7.26
7.03
7.02
6.94
4.34
4.32
4.30
1.80
1.79
1.77
1.75
1.46
1.44
1.42
1.34
1.34
1.33
1.32
0.91
0.90
0.88
0.86
0.88
0.85
1.97
2.01
6.00
2.98
Chemical Shift (ppm)

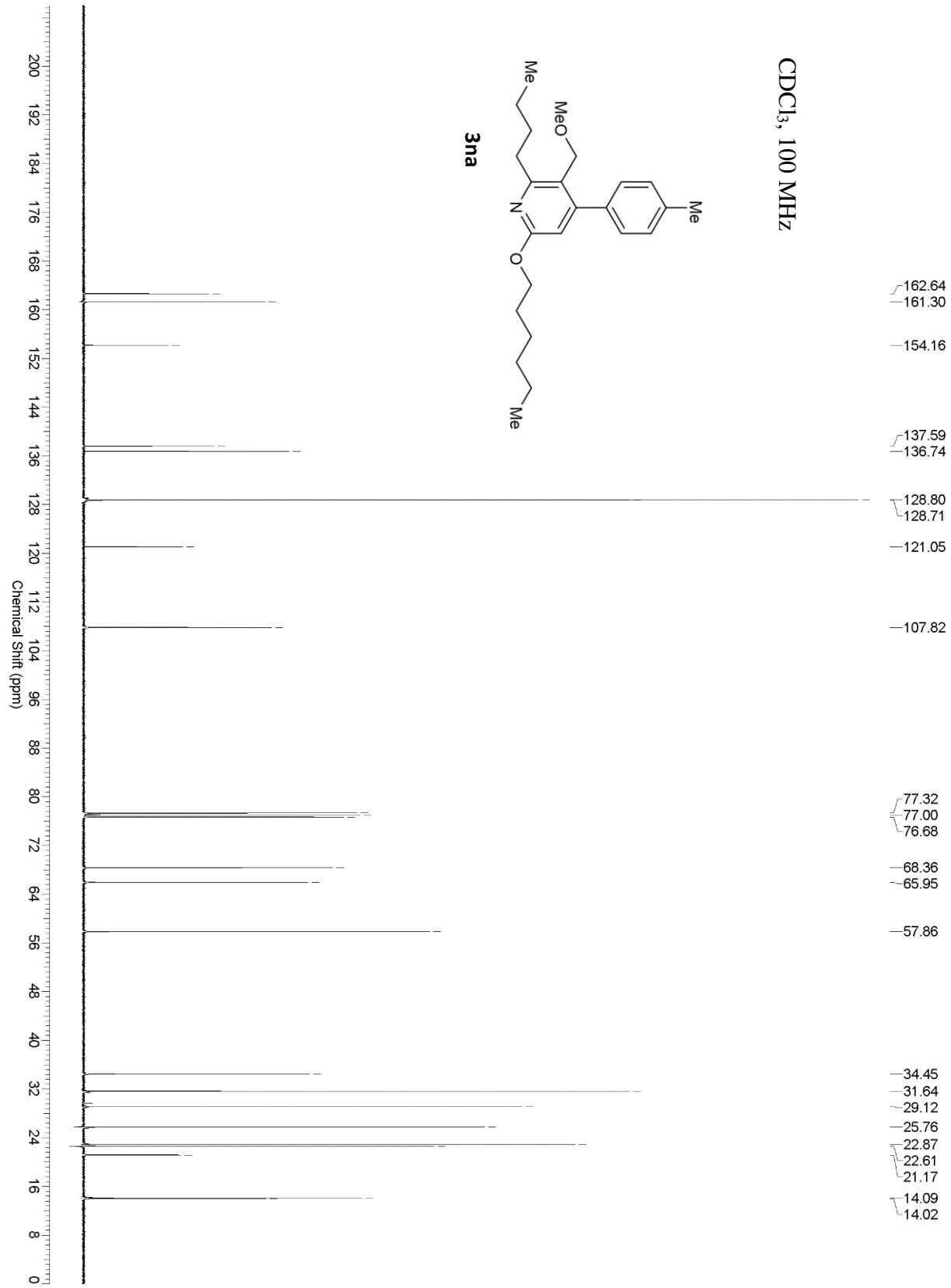

CDCl3, 100 MHz
3ma
CF3
N
O
Me
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
164.48
148.26
141.27
140.93
140.59
140.26
126.79
124.08
121.36
118.64
111.89
111.86
107.78
107.74
77.32
77.00
76.68
66.77
31.57
28.88
25.70
22.60
13.98


CDCl3, 400 MHz
3ma
Br
N
O
Me
7.97
7.95
7.26
7.00
7.00
6.98
6.93
6.93
4.28
4.26
4.24
1.76
1.75
1.73
1.43
1.34
1.33
1.32
1.31
1.25
0.91
0.90
0.90
0.90
0.89
0.88
1.00
0.86
0.84
2.01
2.03
7.09
3.16
Chemical Shift (ppm)

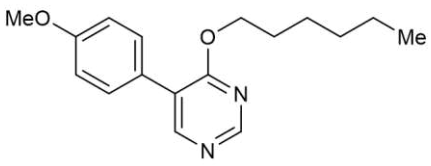
$CDCl_3$, 400 MHz



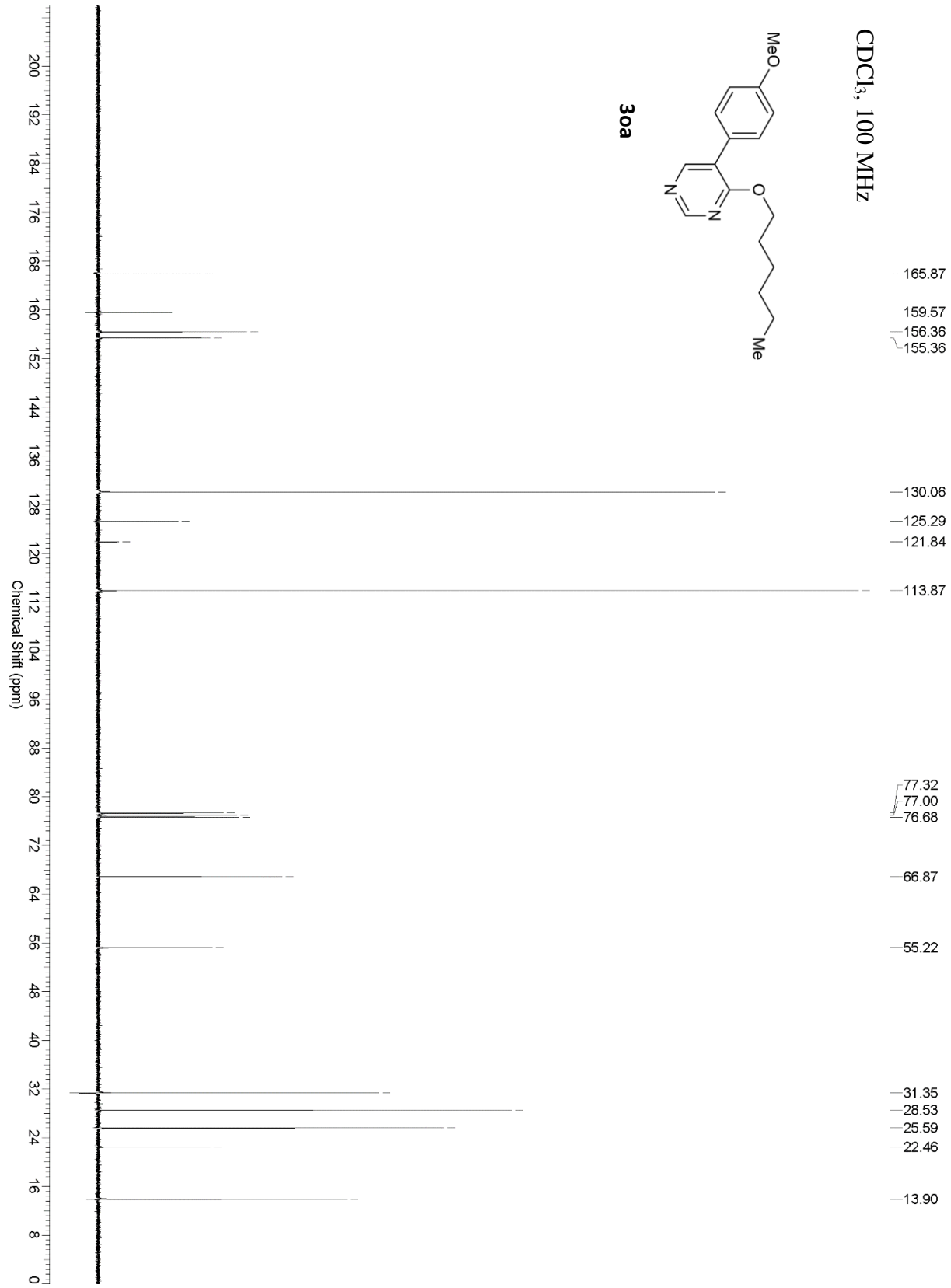
3na

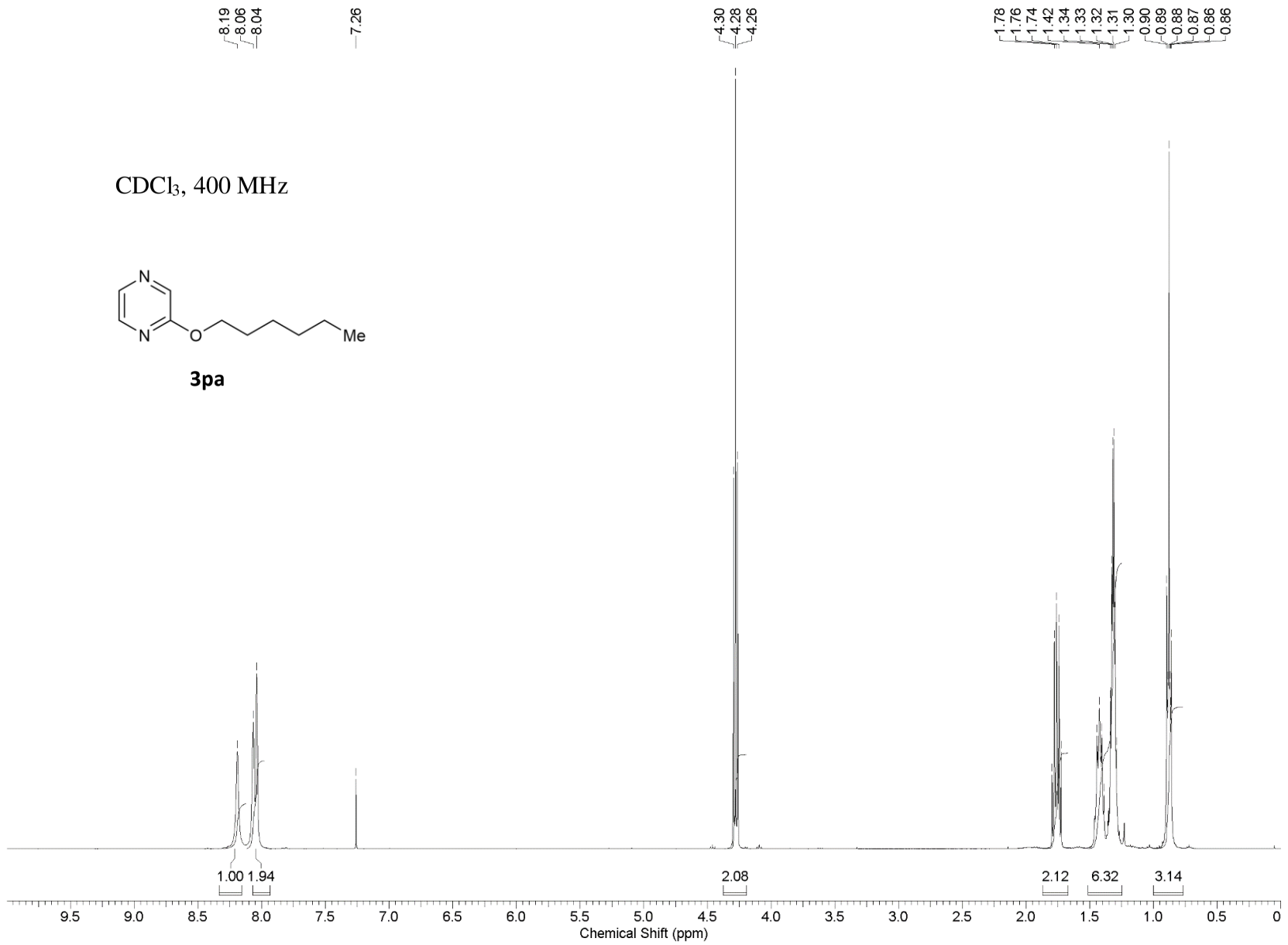

CDCl3, 100 MHz
3na
Me
MeO
N
O
Me
Me
162.64
161.30
154.16
137.59
136.74
128.80
128.71
121.05
107.82
77.32
77.00
76.68
68.36
65.95
57.86
34.45
31.64
29.12
25.76
22.87
22.61
21.17
14.09
14.02
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

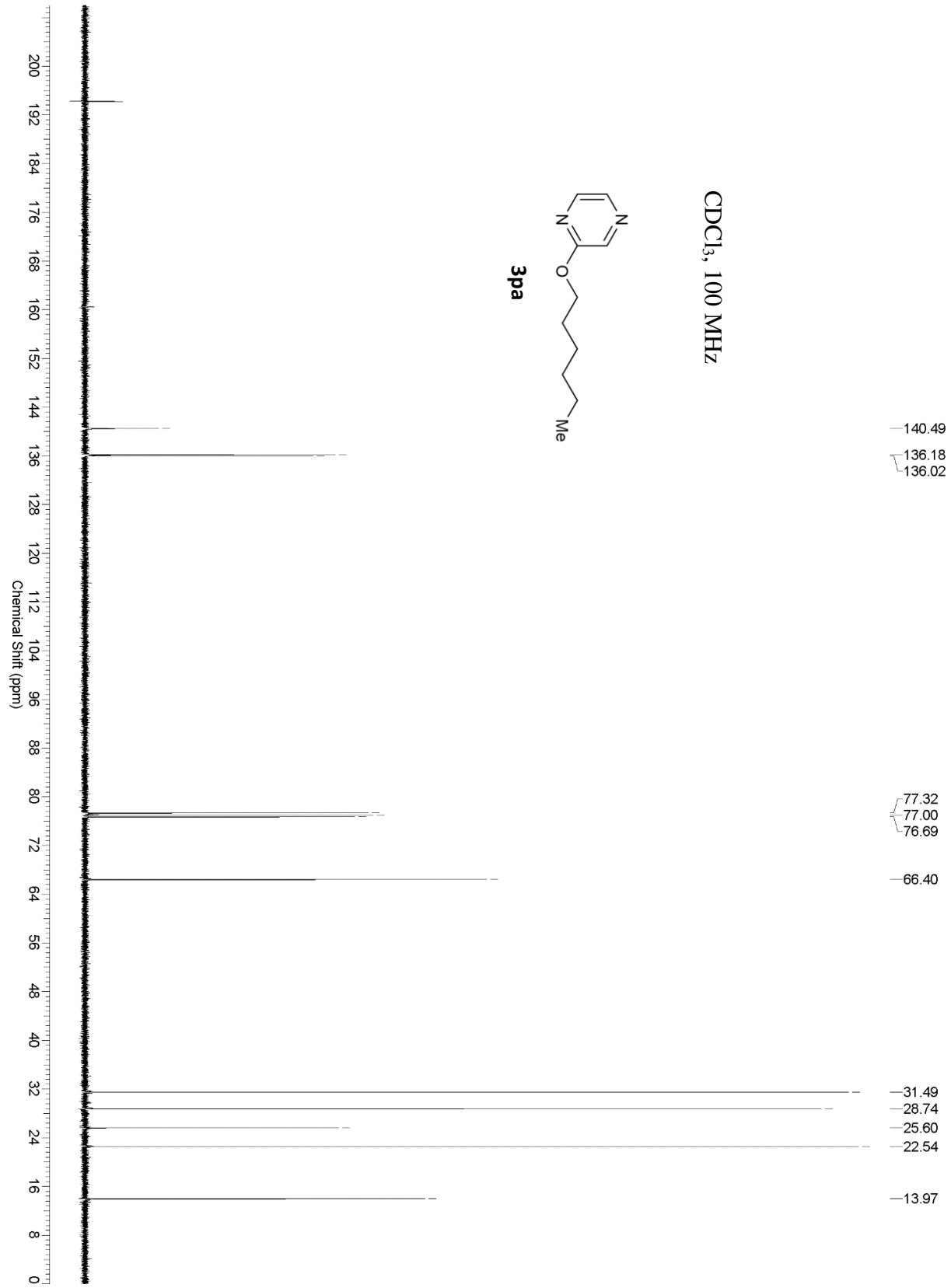
$CDCl_3$, 400 MHz



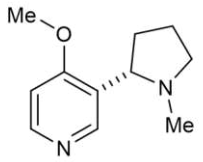
3oa


CDCl3, 100 MHz
3oa
MeO
N
N
O
Me
165.87
159.57
156.36
155.36
130.06
125.29
121.84
113.87
77.32
77.00
76.68
66.87
55.22
31.35
28.53
25.59
22.46
13.90
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

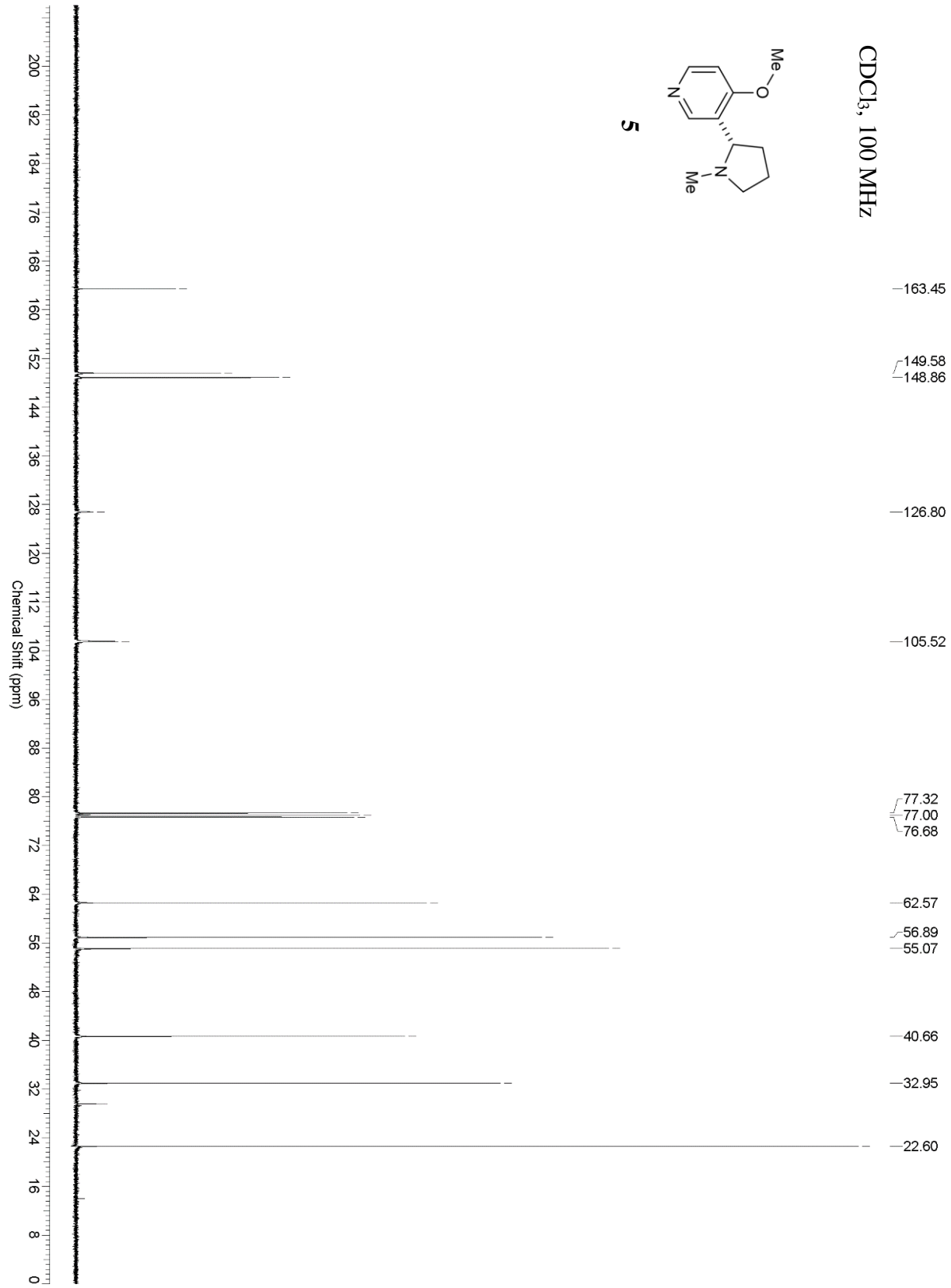

8.19
8.06
8.04
7.26
4.30
4.28
4.26
1.78
1.76
1.74
1.42
1.34
1.33
1.32
1.31
1.30
0.90
0.89
0.88
0.87
0.86
0.86
CDCl3, 400 MHz
N
N
O
Me
3pa
1.00
1.94
2.08
2.12
6.32
3.14
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

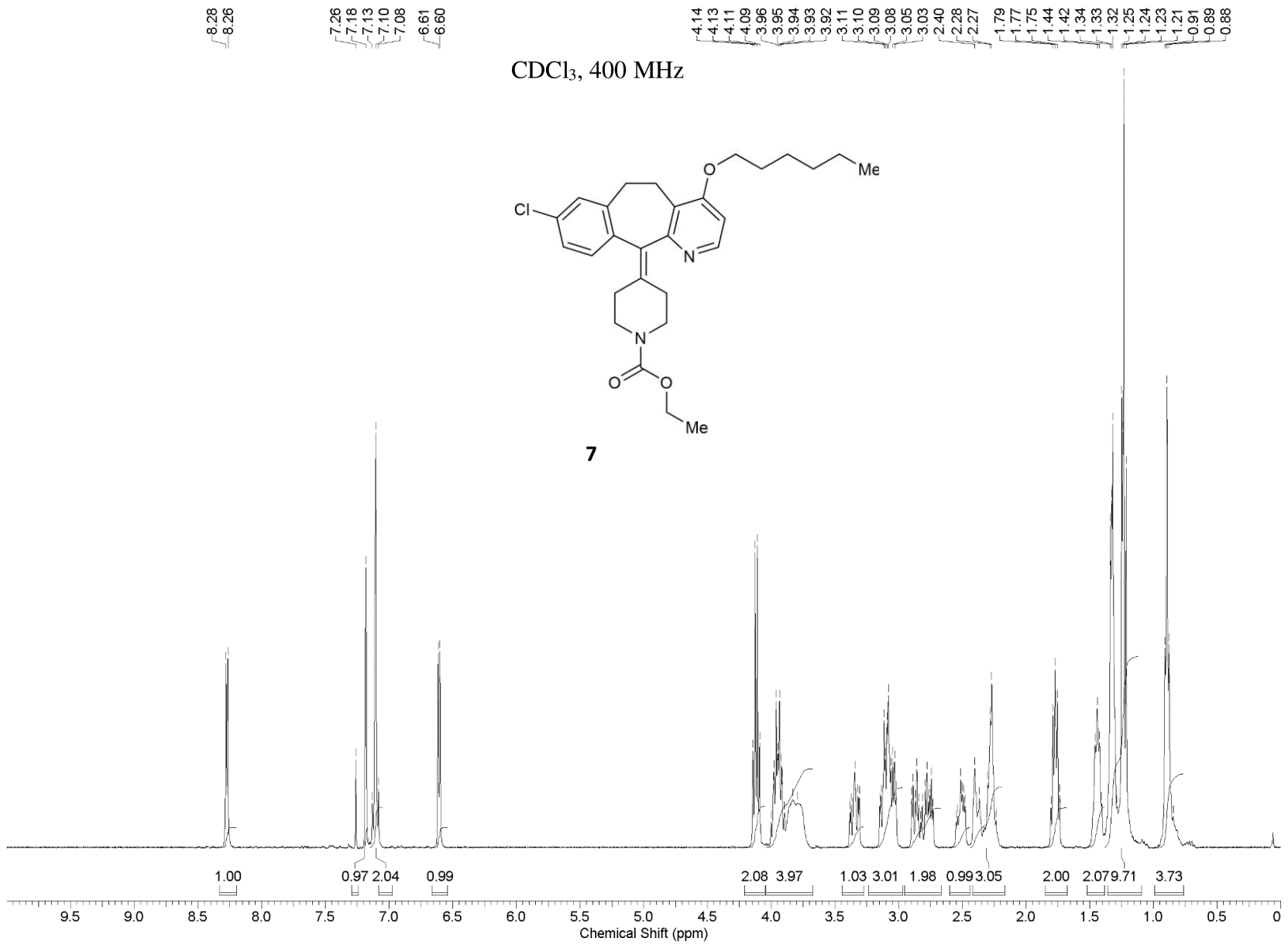

CDCl3, 100 MHz
3pa
N
N
O
Me
140.49
136.18
136.02
77.32
77.00
76.69
66.40
31.49
28.74
25.60
22.54
13.97
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

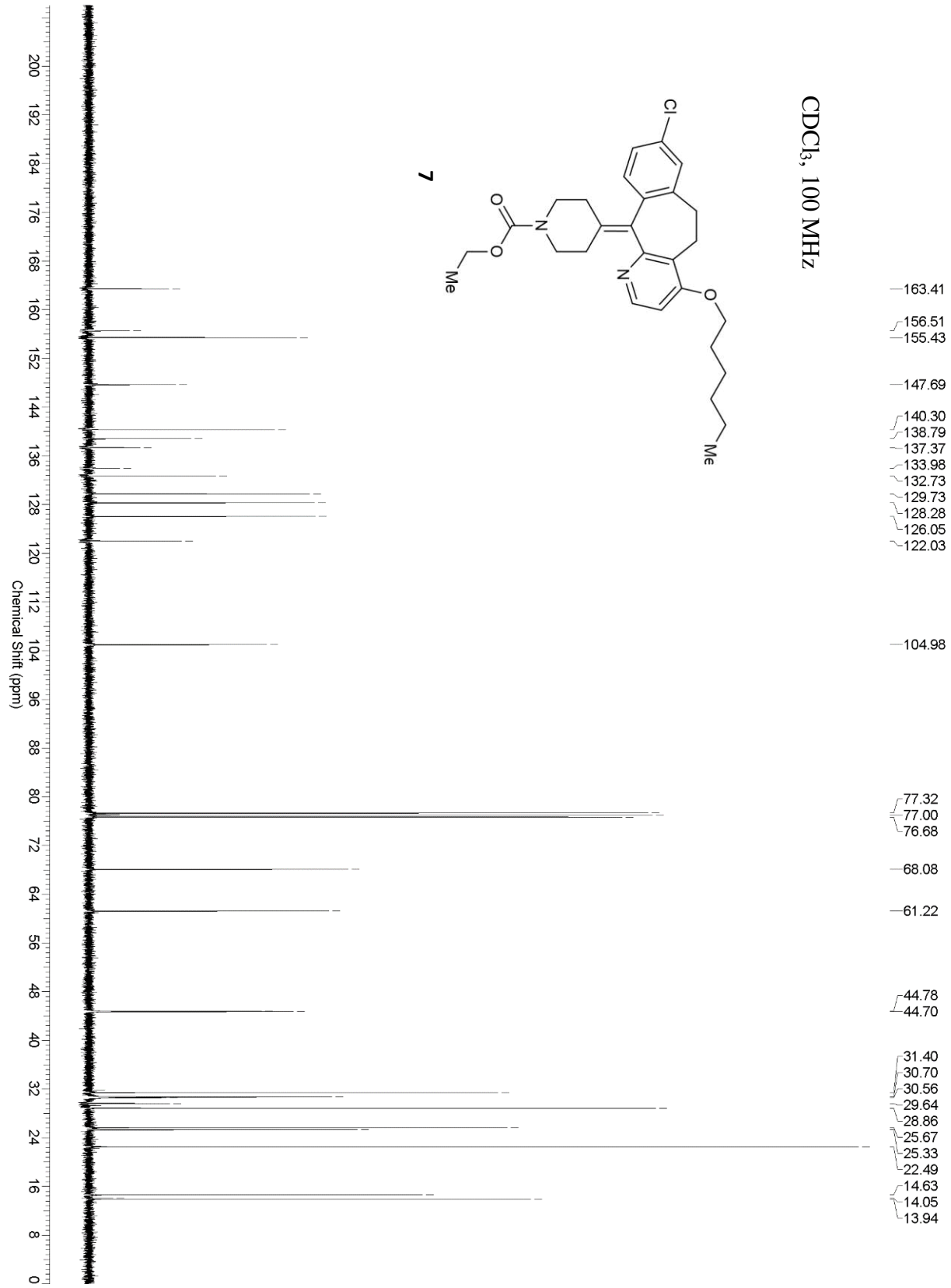
$CDCl_3$, 400 MHz

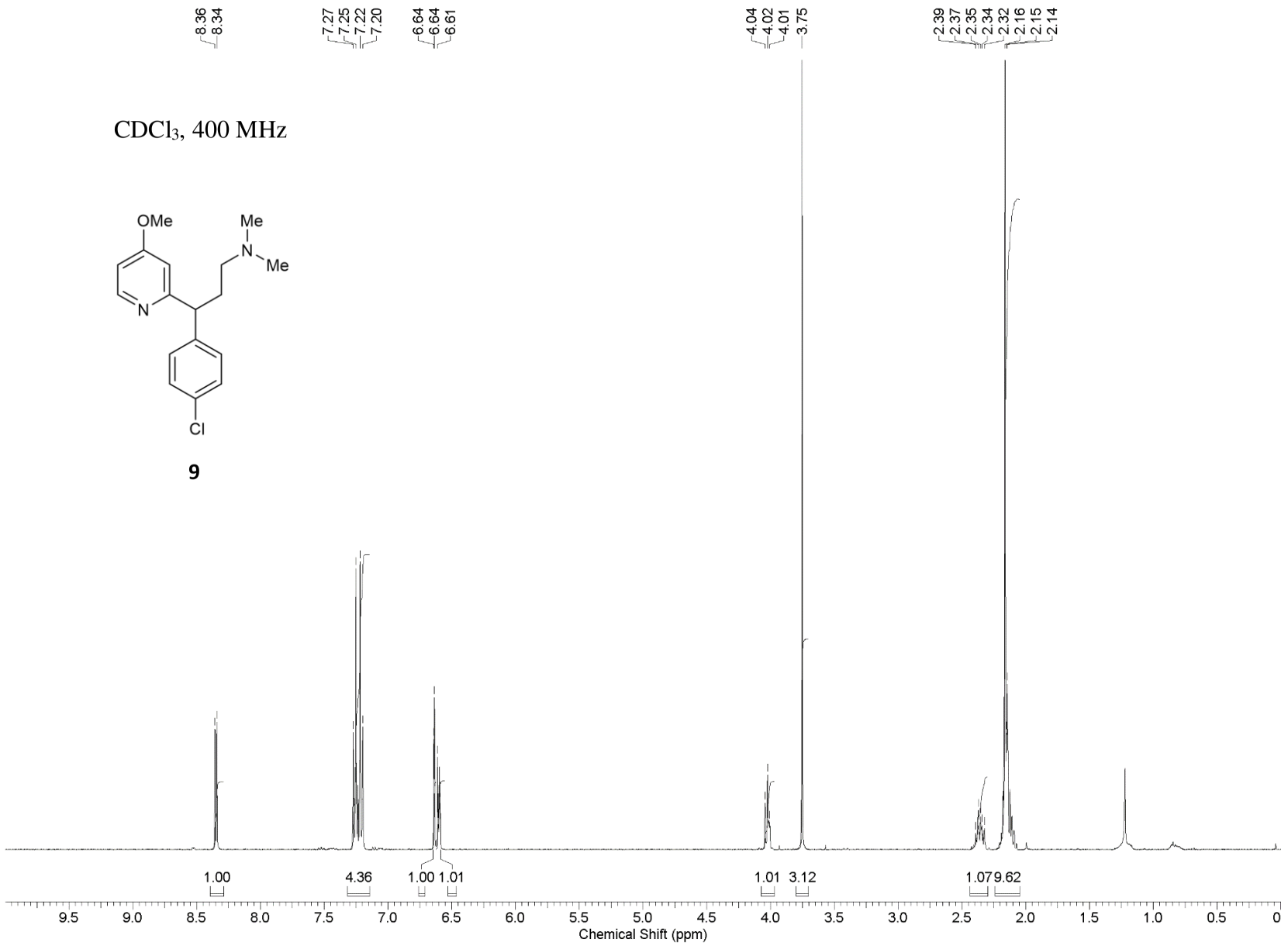


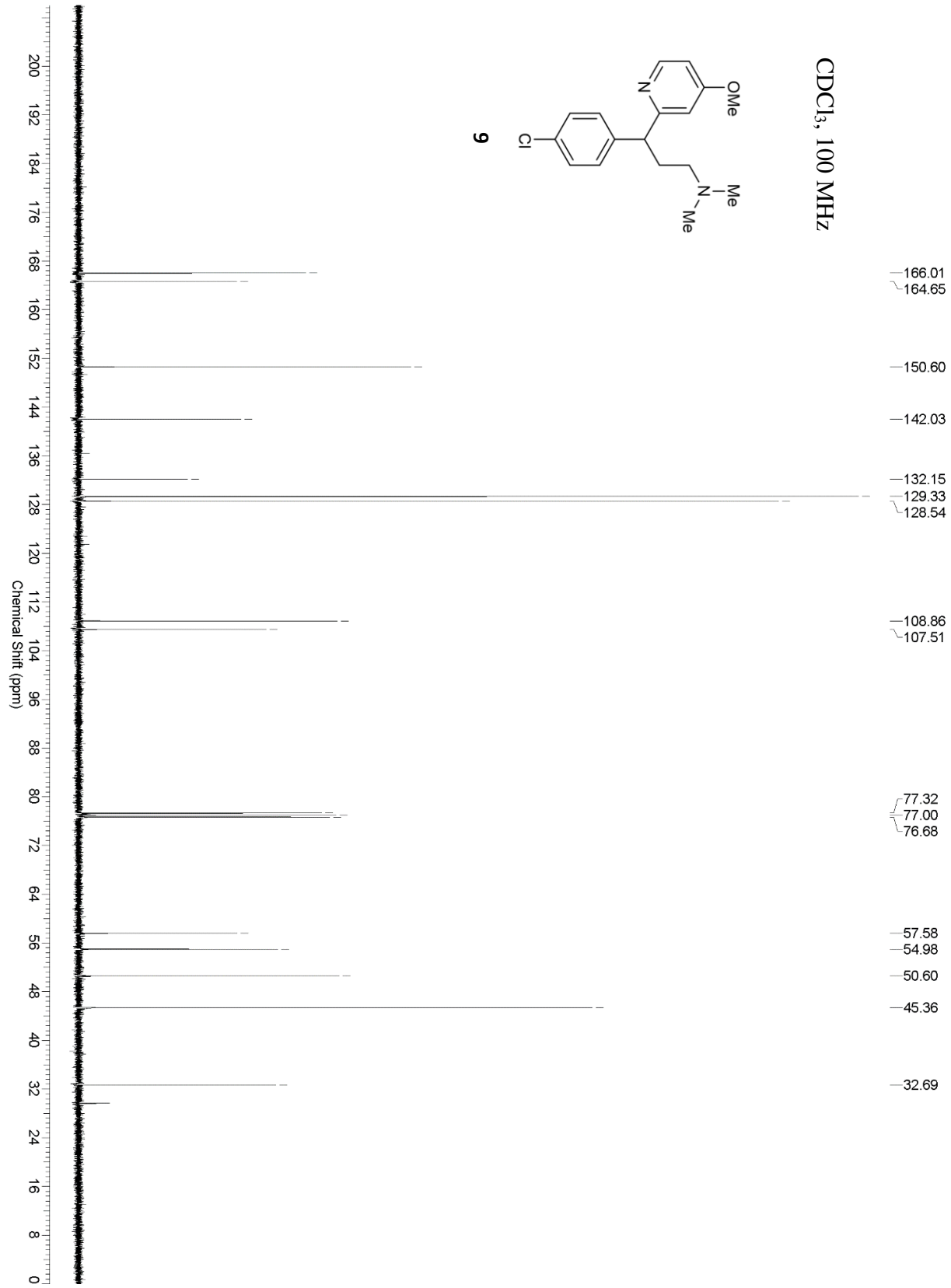
5

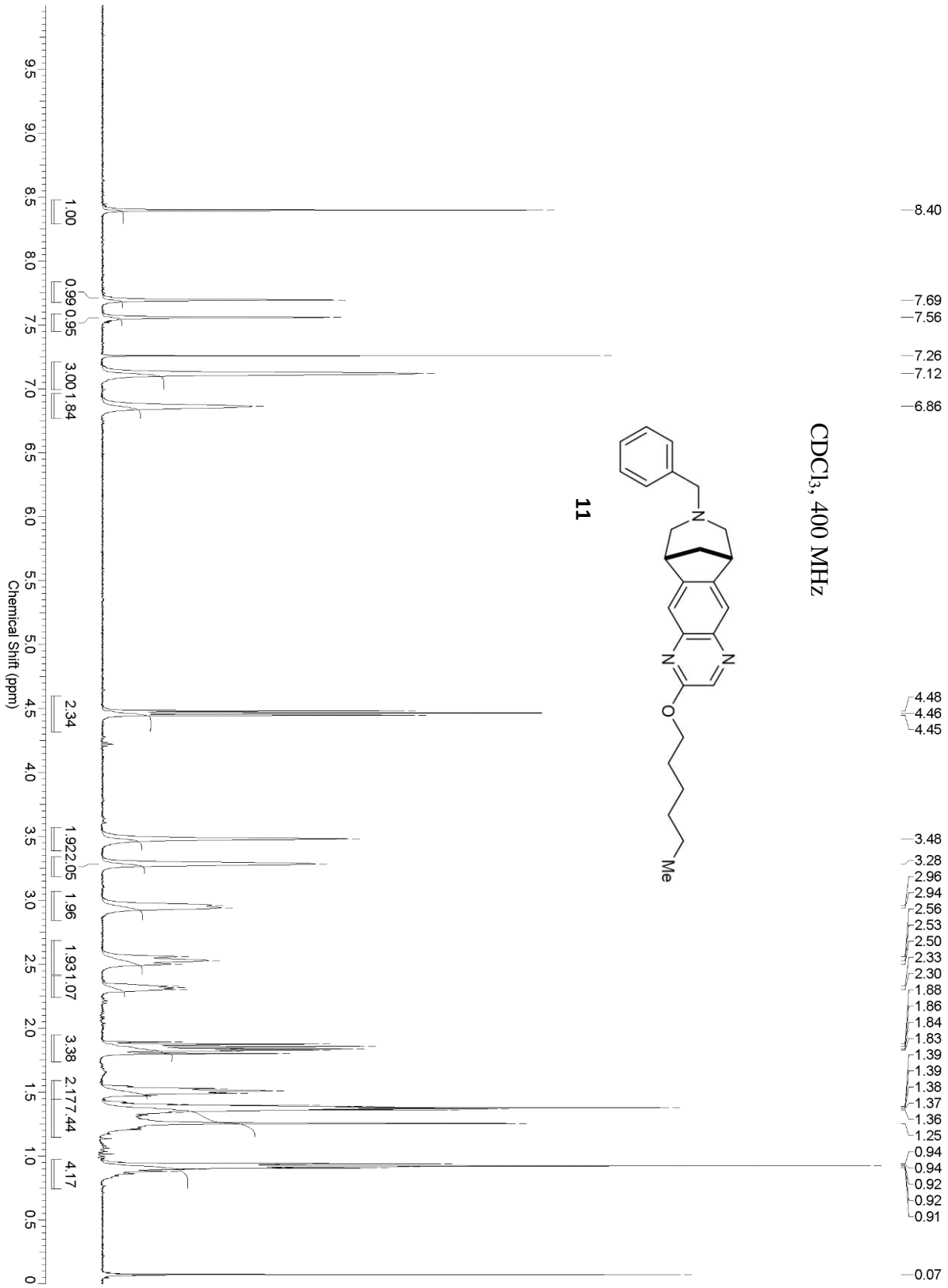

CDCl3, 100 MHz
5
Me
O
N
N
Me
163.45
149.58
148.86
126.80
105.52
77.32
77.00
76.68
62.57
56.89
55.07
40.66
32.95
22.60
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

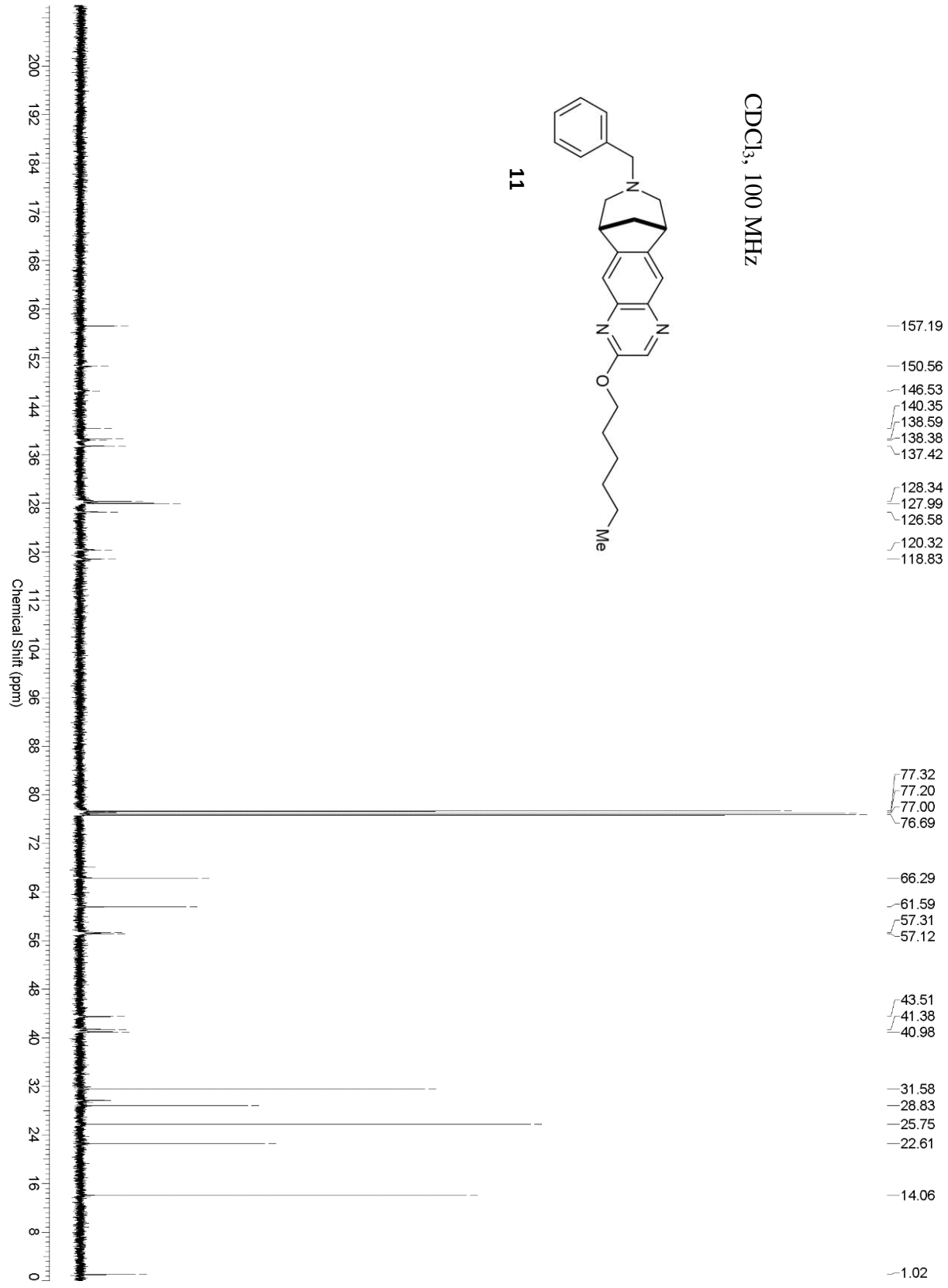

8.28
8.26
7.26
7.18
7.13
7.10
7.08
6.61
6.60
4.14
4.13
4.11
4.09
3.96
3.95
3.94
3.93
3.92
3.11
3.10
3.09
3.08
3.05
3.03
2.40
2.28
2.27
1.79
1.77
1.75
1.44
1.42
1.34
1.33
1.32
1.25
1.24
1.23
1.21
0.91
0.89
0.88
CDCl3, 400 MHz
Cl
O
Me
N
N
O
O
Me
7
1.00
0.97
2.04
0.99
2.08
3.97
1.03
3.01
1.98
0.99
3.05
2.00
2.07
9.71
3.73
Chemical Shift (ppm)

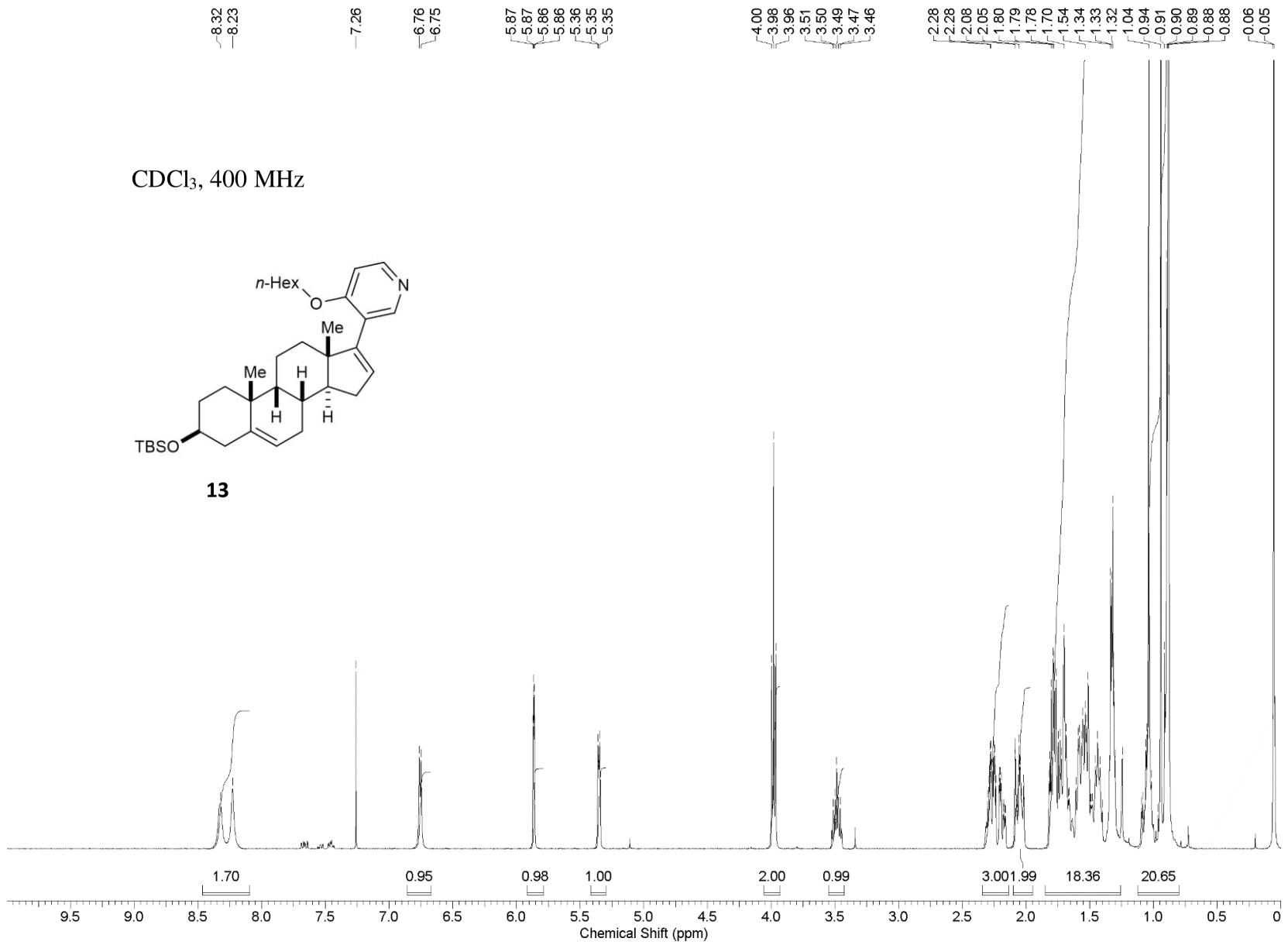

CDCl3, 100 MHz
7
Cl
N
O
O
N
Me
N
O
Me
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
163.41
156.51
155.43
147.69
140.30
138.79
137.37
133.98
132.73
129.73
128.28
126.05
122.03
104.98
77.32
77.00
76.68
68.08
61.22
44.78
44.70
31.40
30.70
30.56
29.64
28.86
25.67
25.33
22.49
14.63
14.05
13.94

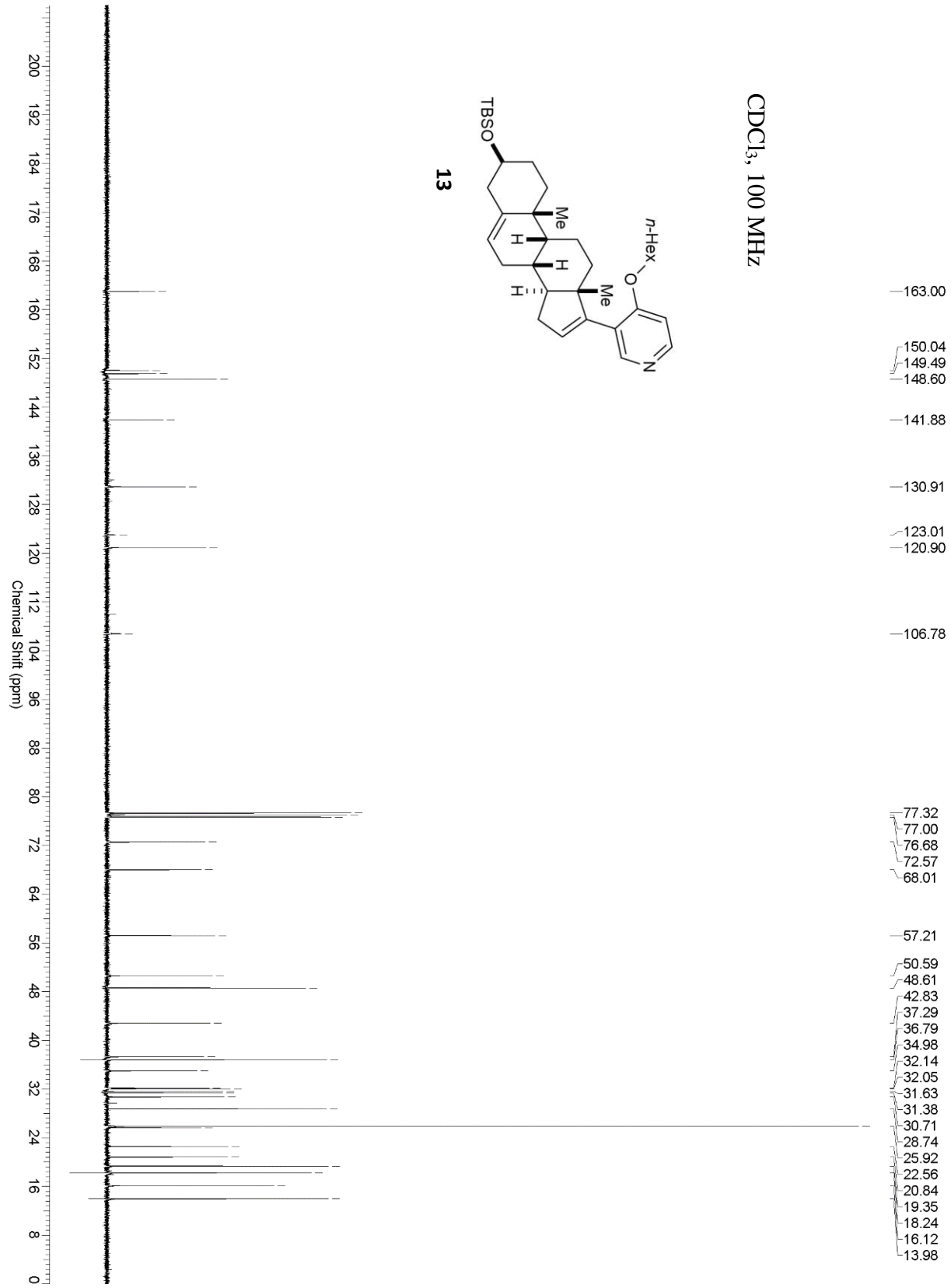

8.36
8.34
7.27
7.25
7.22
7.20
6.64
6.64
6.61
4.04
4.02
4.01
3.75
2.39
2.37
2.35
2.34
2.32
2.16
2.15
2.14
CDCl3, 400 MHz
OMe
Me
N
Me
N
Cl
9
1.00
4.36
1.00
1.01
1.01
3.12
1.07
9.62
Chemical Shift (ppm)

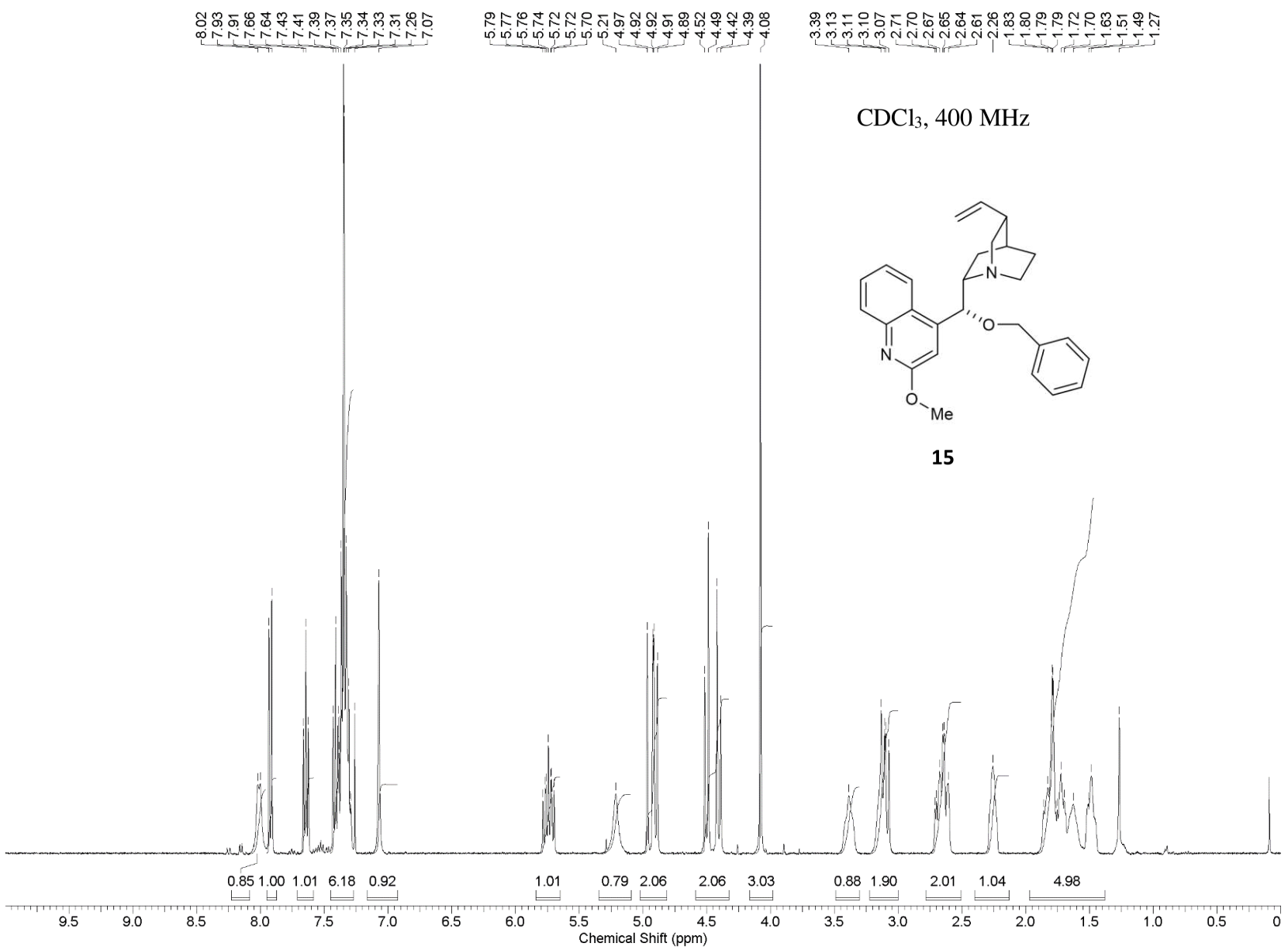

CDCl3, 100 MHz
9
OMe
N
Cl
N
Me
Me
166.01
164.65
150.60
142.03
132.15
129.33
128.54
108.86
107.51
77.32
77.00
76.68
57.58
54.98
50.60
45.36
32.69
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0


CDCl3, 400 MHz
11
Me
Chemical Shift (ppm)
8.40
7.69
7.56
7.26
7.12
6.86
4.48
4.46
4.45
3.48
3.28
2.96
2.94
2.56
2.53
2.50
2.33
2.30
1.88
1.86
1.84
1.83
1.39
1.39
1.38
1.37
1.36
1.25
0.94
0.94
0.92
0.92
0.91
0.07
1.00
0.99
0.95
3.00
1.84
2.34
1.92
2.05
1.96
1.93
1.07
3.38
2.17
7.44
4.17

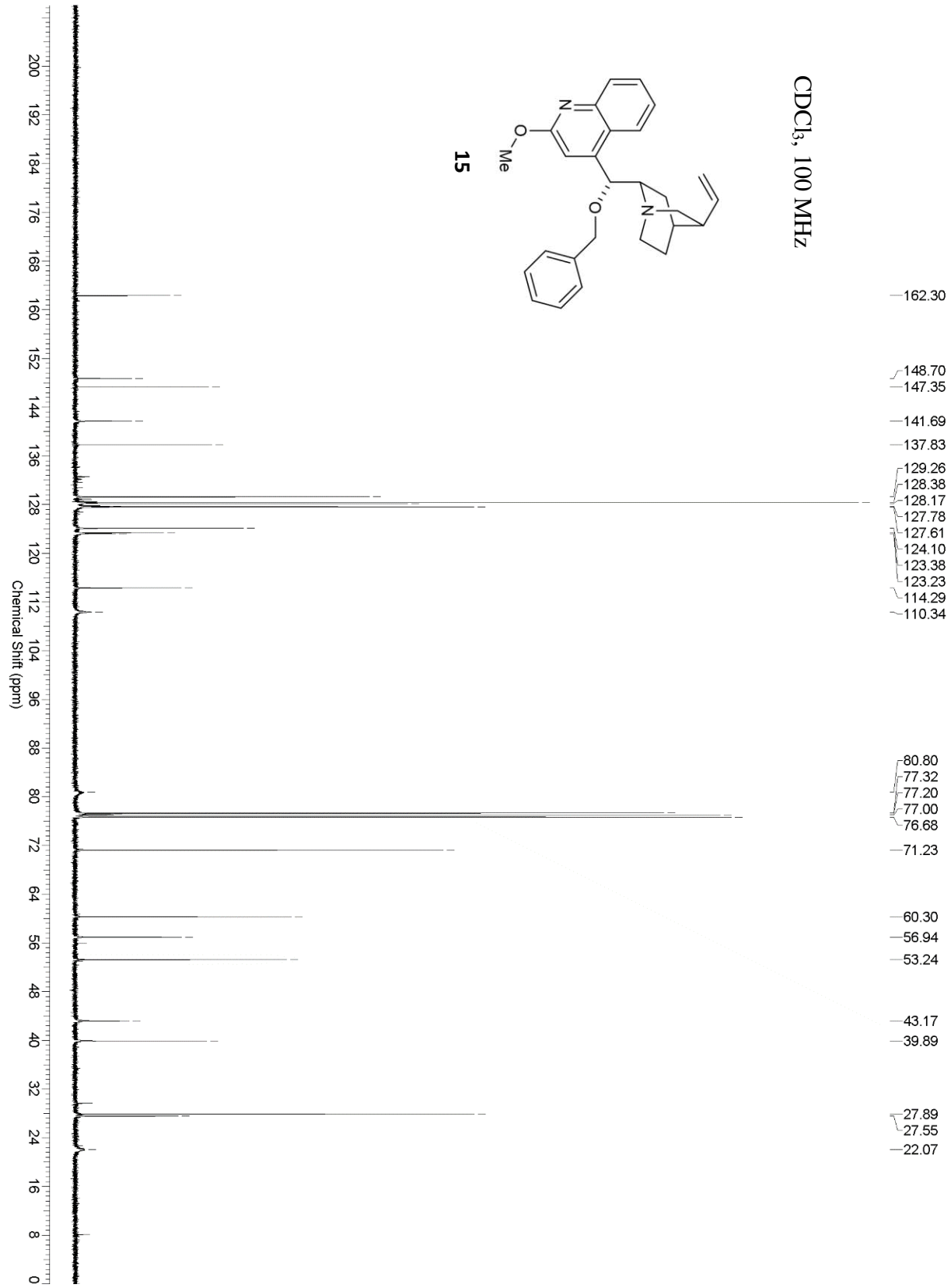

CDCl3, 100 MHz
11
Me
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
157.19
150.56
146.53
140.35
138.59
138.38
137.42
128.34
127.99
126.58
120.32
118.83
77.32
77.20
77.00
76.69
66.29
61.59
57.31
57.12
43.51
41.38
40.98
31.58
28.83
25.75
22.61
14.06
1.02


8.32
8.23
7.26
6.76
6.75
5.87
5.87
5.86
5.86
5.36
5.35
5.35
4.00
3.98
3.96
3.51
3.50
3.49
3.47
3.46
2.28
2.28
2.08
2.05
1.80
1.79
1.78
1.70
1.54
1.34
1.33
1.32
1.04
0.94
0.91
0.90
0.89
0.88
0.88
0.06
0.05
CDCl3, 400 MHz
n-Hex
O
N
Me
Me
H
H
H
TBSO
13
1.70
0.95
0.98
1.00
2.00
0.99
3.00
1.99
18.36
20.65
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


CDCl3, 100 MHz
13
TBSO
Me
H
H
H
Me
n-Hex
O
N
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
163.00
150.04
149.49
148.60
141.88
130.91
123.01
120.90
106.78
77.32
77.00
76.68
72.57
68.01
57.21
50.59
48.61
42.83
37.29
36.79
34.98
32.14
32.05
31.63
31.38
30.71
28.74
25.92
22.56
20.84
19.35
18.24
16.12
13.98


8.02
7.93
7.91
7.66
7.64
7.43
7.41
7.39
7.37
7.35
7.34
7.33
7.31
7.26
7.07
5.79
5.77
5.76
5.74
5.72
5.72
5.70
5.21
4.97
4.92
4.92
4.91
4.89
4.52
4.49
4.42
4.39
4.08
3.39
3.13
3.11
3.10
3.07
2.71
2.70
2.67
2.65
2.64
2.61
2.26
1.83
1.80
1.79
1.79
1.72
1.70
1.63
1.51
1.49
1.27
CDCl3, 400 MHz
N
O
N
O
Me
0.85 1.00 1.01 6.18 0.92
1.01
0.79 2.06
2.06
3.03
0.88 1.90
2.01
1.04
4.98
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

15


CDCl3, 100 MHz
15
O
Me
N
N
O
162.30
148.70
147.35
141.69
137.83
129.26
128.38
128.17
127.78
127.61
124.10
123.38
123.23
114.29
110.34
80.80
77.32
77.20
77.00
76.68
71.23
60.30
56.94
53.24
43.17
39.89
27.89
27.55
22.07
Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

APPENDIX TWO

Bis-Heterobiaryl Formation using Phosphorus Ligand-Coupling: Experimental

(Combined Work of Xuan Zhang, Ben Boyle and Michael Hilton)

A 2.1 General Methods and Materials

Tf_2O (99%) was purchased from Oakwood Chemical and used without further purification but was routinely stored in a –20 ºC fridge. DBU was distilled before use. (2,2,2)-Trifluoroethanol (TFE) was purchased from Oakwood Chemicals and used without further purification. 200 proof ethanol was purchased from PHARMCO-AAPER and used without further purification. HCl (4.0 M in dioxanes) and trifluoromethanesulfonic acid (98%) were purchased from Sigma Aldrich chemical company and used without further purification but were routinely stored in a –20 ºC fridge. All reactions were run under a nitrogen atmosphere unless otherwise noted.

A 2.2 Instrumentation

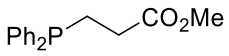
^{1}H NMR spectra were recorded using a Varian 400 MR spectrometer, an Agilent Inova 400 spectrometer, an Agilent Inova 500 spectrometer, or a Bruker AV-111 400 spectrometer. The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: $CDCl_3$ (7.26 ppm), $(CD_3)_2SO$ (2.50 ppm), or CD_3OD (3.31 ppm). Coupling constants (*J*) were reported in Hertz (Hz) and the multiplicity was reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. ^{13}C NMR spectra were recorded using a Bruker Ultrashield–400, a Varian 400 MR or an Agilent Inova 400 spectrometer.

The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: $CDCl_3$ (77.00 ppm), $(CD_3)_2SO$ (39.51 ppm), or CD_3OD (49.00 ppm). Low–resolution mass spectra were recorded on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared spectra were recorded on a Bruker Tensor 27 FT–IR spectrometer with absorptions reported in wavenumbers (cm^{-1}). Melting points were recorded using a Büchi B–450 melting point apparatus.

A 2.3. General Procedures

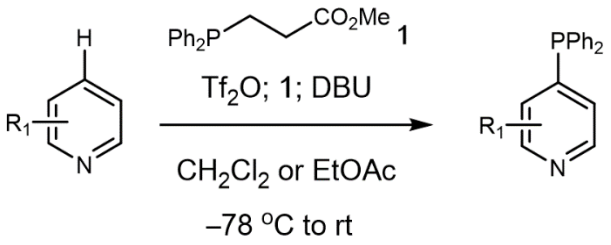
A 2.3.1 Synthesis of the Fragmentable Phosphine

Methyl 3-(diphenylphosphaneyl)propanoate (1)



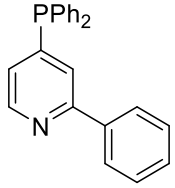
An oven-dried round bottomed flask was charged with diphenylphosphane (17.4 mL, 100 mmol) under a nitrogen atmosphere. Methyl acrylate (9.0 mL, 100 mmol), previously degassed via N_2 sparging, was added dropwise at room temperature over 15 minutes. The reaction was stirred for 16 hours at room temperature before concentrating *in vacuo*. The crude material was purified by flash chromatography (silica gel: 9% EtOAc in hexanes) afforded the title compound as a colorless oil (24.26 g, 89.10 mmol, 89% yield). IR ν_{max}/cm^{-1} (film): 3053, 2949, 1735, 1481, 1433, 1353, 1221, 1164, 736, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47-7.39 (4H, m), 7.38-7.30 (6H, m), 3.65 (3H, s), 2.46-2.31 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.05 (d, J = 15.3 Hz), 137.52 (d, J = 13.0 Hz), 132.39 (d, J = 19.2 Hz), 128.47, 128.22 (d, J = 6.6 Hz), 51.33, 30.21 (d, J = 19.8 Hz), 22.69 (d, J =12.2 Hz); ^{31}P (162 MHz, $CDCl_3$) δ: –15.76; *m/z* HRMS (DART) found $[M+H]^+$ 273.1057, $C_{16}H_{18}O_2P^+$ requires 273.1039.

A 2.3.2 General Procedure A (Preparation of Heteroaryl Phosphines)



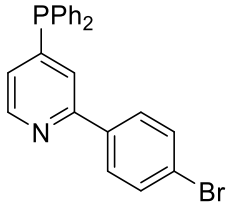
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before the mixture was warmed to –50 ºC and then methyl 3-(diphenylphosphaneyl)propanoate (1.1 equiv) was added dropwise as a solution (2.0 M in CH_2Cl_2). The reaction was subjected to three rapid cycles of vacuum / nitrogen backfill and was stirred for a further 30 minutes at –50 ºC. The reaction was cooled to –78 ºC and DBU (3.0 equiv) was added dropwise via syringe, the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring for approximately 2 hours. The reaction was diluted with H_2O and then extracted with CH_2Cl_2 (3x). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl phosphine product.

4-(Diphenylphosphaneyl)-2-phenylpyridine (2a)



Prepared according to general procedure A using 2-phenylpyridine (2.13 mL, 14.90 mmol), Tf_2O (2.50 mL, 14.90 mmol), methyl 3-(diphenylphosphaneyl)propanoate (4.44 g, 16.30 mmol), DBU (6.67 mL, 44.70 mmol) and CH_2Cl_2 (149 mL). Crude (to determine the inherent regioselectivity a separate reaction was ran with 1eq DBU instead of 3eq resulting in a pre-fragmented phosphonium salt. See crude ^{31}P NMR for structure) regiomeric ratio 13.3:1.0 (4-position:2-position). Flash column chromatography (silica gel, gradient elution: 1% Et_2O in toluene to 2.5% Et_2O in toluene) afforded the title compound as a white solid (3.59 g, 10.57 mmol, 71% yield). mp 73-74 ºC; IR ν_{max}/cm^{-1} (film): 3053, 1570, 1434, 1373, 1026, 907, 837, 733, 693; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, dd, *J* = 5.1, 2.4 Hz), 7.92 (2H, d, *J* = 7.5 Hz), 7.65 (1H, d, *J* = 7.5 Hz) 7.50-7.35 (13H, m), 7.06 (1H, dd, *J* = 6.2, 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.79 (d, *J* = 5.1 Hz), 149.48 (d, *J* = 17.5 Hz), 149.12 (d, *J* = 4.2 Hz), 139.04, 134.93 (d, *J* = 10.1 Hz), 134.09 (d, *J* = 20.4 Hz), 129.44, 128.94, 128.76 (d, *J* = 7.5 Hz), 128.62, 126.86, 125.48 (d, *J* = 13.5 Hz), 124.13 (d, *J* = 18.0 Hz); ^{31}P (162 MHz, $CDCl_3$) δ: -6.38; *m/z* HRMS (DART) found $[M+H]^+$ 340.1271, $C_{23}H_{19}NP^+$ requires 340.1250.

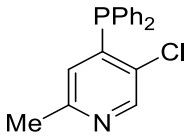
2-(4-Bromophenyl)-4-(diphenylphosphaneyl)pyridine (2b)



Prepared according to general procedure A using 2-(4-bromophenyl)pyridine (2.20 g, 9.40 mmol), Tf_2O (1.58 mL, 9.40 mmol), methyl 3-(diphenylphosphaneyl)propanoate (2.82 g, 10.34 mmol), DBU (4.21 mL, 28.20 mmol) and CH_2Cl_2 (94 mL). Crude (to determine the inherent regioselectivity a separate reaction was ran with 1eq DBU instead of 3eq resulting in a pre-

fragmented phosphonium salt. See crude ^{31}P NMR for structure.) regiomeric ratio 13.9:1.0 (4-position:2-position). Flash column chromatography (silica gel: 1% ether in toluene) afforded the title compound as a white solid (2.40 g, 5.75 mmol, 61% yield). mp 120-123 ºC; IR ν_{max}/cm^{-1} (film): 3056, 1580, 1462, 1431, 1403, 1366, 1070, 826, 741, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.61 (1H, dd, *J* = 5.0, 2.4 Hz), 7.79 (2H, d, *J* = 8.6 Hz), 7.61 (1H, d, *J* = 7.3 Hz), 7.55 (2H, d, *J* = 8.6 Hz), 7.48-7.36 (10H, m), 7.06 (1H, t, *J* = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.52 (d, *J* = 5.3 Hz), 149.85 (d, *J* = 18.3 Hz), 149.12 (d, *J* = 4.1 Hz), 137.81, 134.77 (d, *J* = 9.9 Hz), 134.07 (d, *J* = 20.6 Hz), 131.70, 129.49, 128.78 (d, *J* = 7.6 Hz), 128.37, 125.73 (d, *J* = 13.0 Hz), 123.77 (d, *J* = 18.4 Hz), 123.45; ^{31}P (162 MHz, $CDCl_3$) δ: -6.35; *m/z* HRMS (DART) found $[M+H]^+$ 418.1046, $C_{23}H_{18}BrNP^+$ requires 418.1036.

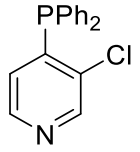
5-Chloro-4-(diphenylphosphino)-2-methylpyridine (2c)



Prepared according to general procedure A using 5-chloro-2-methylpyridine (333 mg, 2.60 mmol), Tf_2O (437 μL, 2.60 mmol), methyl 3-(diphenylphosphino)propanoate (779 mg, 2.86 mmol), DBU (1.17 mL, 7.80 mmol) and CH_2Cl_2 (26 mL). Flash chromatography (silica gel: 9% EtOAc in hexanes to 16% EtOAc in hexanes) afforded the title compound as a white amorphous powder (524 mg, 1.69 mmol, 65% yield). mp 112–114 °C; IR υ_{max}/cm^{-1} (film): 3052, 2990, 2921, 1563, 1477, 1441, 1434, 1323, 1127, 749, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (1H, d, *J* = 4.5 Hz), 7.44–7.37 (6H, m), 7.32–7.28 (4H, m), 6.48 (1H, d, *J* = 3.0 Hz), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.39, 148.01, 147.45 (d, *J* = 19.8 Hz), 134.15 (d, *J* = 20.7 Hz), 133.52 (d, *J* = 8.9 Hz), 133.28 (d, *J* = 22.2 Hz), 129.58, 128.87 (d, *J* = 7.6 Hz), 126.91, 23.93; ^{31}P NMR (162

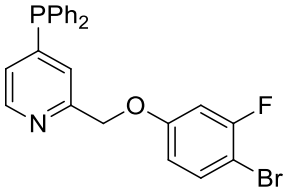
MHz, $CDCl_3$) δ: −11.81; *m/z* HRMS (DART) found $[M+H]^+$ 312.0710, $C_{18}H_{16}ClNP^+$ requires 312.0709.

3-Chloro-4-(diphenylphosphino)pyridine (2d)



Prepared according to general procedure A using 3-chloropyridine (380 μL, 4.00 mmol), Tf_2O (672 μL, 4.00 mmol), methyl 3-(diphenylphosphino)propanoate (1.20 g, 4.40 mmol), DBU (1.80 mL, 12.00 mmol) and CH_2Cl_2 (40 mL). Flash chromatography (silica gel: CH_2Cl_2 to 5% EtOAc in CH_2Cl_2 afforded the title compound as a white powder (1.08 g, 3.64 mmol, 91% yield). mp 66-68 °C; IR υ_{max}/cm^{-1} (film): 3047, 1568, 1478, 1447, 1433, 1392, 1265, 1181, 1119, 1095, 1077, 1029, 836, 744; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, *J* = 4.4 Hz), 8.32 (1H, dd, *J* = 4.9, 0.8 Hz), 7.46–7.36 (6H, m), 7.34–7.27 (4H, m), 6.64 (1H, ddd, *J* = 5.0, 2.8, 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.85, 147.70 (d, *J* = 20.5 Hz), 147.34, 136.20 (d, *J* = 22.2 Hz), 134.14 (d, *J* = 20.9 Hz), 133.29 (d, *J* = 9.1 Hz), 129.66, 128.91 (d, *J* = 7.8 Hz), 127.35; ^{31}P NMR (162 MHz, $CDCl_3$) δ: −11.94; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 298.1, $C_{17}H_{14}ClNP^+$ requires 298.1.

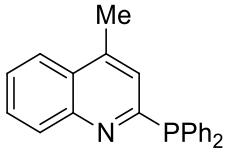
2-((4-Bromo-3-fluorophenoxy)methyl)-4-(diphenylphosphino)pyridine (2e)



Prepared according to general procedure A using 2-((4-bromo-3-fluorophenoxy)methyl)pyridine (1.41 g, 5.00 mmol), Tf_2O (840 μL, 5.00 mmol), methyl 3-

(diphenylphosphino)propanoate (1.50 g, 5.50 mmol), DBU (2.25 mL, 15.00 mmol) and CH_2Cl_2 (50 mL). Flash chromatography (silica gel: 16% EtOAc in hexanes) afforded the title compound as a white amorphous powder (1.96 g, 4.20 mmol, 84% yield). mp 125–127 °C; IR υ_{max}/cm^{-1} (film): 3091, 3068, 2915, 1603, 1580, 1540, 1490, 1476, 1470, 1447, 1435, 1431, 1375, 1294, 1242, 1168, 1149, 1094, 1062, 1027, 991, 949, 887, 853, 831, 804, 747, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50–8.48 (1H, m), 7.42–7.27 (11H, m), 7.22–7.20 (1H, m), 7.05–7.02 (1H, m), 6.64 (1H, dd, *J* = 10.2, 2.8 Hz), 6.56 (1H, ddd, *J* = 8.9, 2.8, 1.0 Hz), 5.13 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.36 (d, *J* = 245.5 Hz), 158.60 (d, *J* = 9.7 Hz), 155.60 (d, *J* = 4.2 Hz), 150.34 (d, *J* = 18.4 Hz), 148.87 (d, *J* = 4.3 Hz), 134.60 (d, *J* = 9.8 Hz), 134.12 (d, *J* = 20.4 Hz), 133.32 (d, *J* = 1.9 Hz), 129.58, 128.83 (d, *J* = 7.5 Hz), 126.30 (d, *J* = 14.9 Hz), 124.69 (d, *J* = 15.9 Hz), 112.01 (d, *J* = 3.2 Hz), 104.02 (d, *J* = 25.4 Hz), 99.87 (d, *J* = 21.2 Hz), 70.83; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -105.03 (t, *J* = 8.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: –6.50; *m/z* HRMS (DART) found $[M+H]^+$ 466.0399, $C_{24}H_{19}BrFNOP^+$ requires 466.0372.

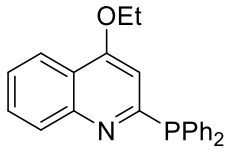
2-(Diphenylphosphino)-4-methylquinoline (2f)



Prepared according to general procedure A using 4-methylquinoline (793 μL, 6.00 mmol), Tf_2O (1.01 mL, 6.00 mmol), methyl 3-(diphenylphosphino)propanoate (1.80 g, 6.60 mmol), DBU (2.70 mL, 18.00 mmol) and CH_2Cl_2 (60 mL). Flash chromatography (silica gel: 16% EtOAc in hexanes) afforded the title compound as a white amorphous powder (1.63 g, 4.98 mmol, 83% yield). mp 99–102 °C; IR υ_{max}/cm^{-1} (film): 3058, 2953, 2926, 2858, 1727, 1576, 1541, 1497, 1479, 1444, 1435, 1431, 761, 751, 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (1H, d, *J* = 8.4 Hz), 7.96

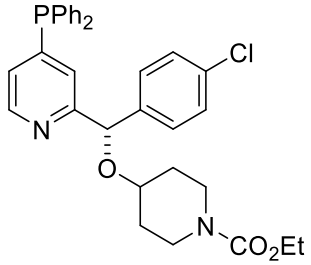
(1H, d, J = 8.3 Hz), 7.72–7.68 (1H, m), 7.58–7.54 (1H, m), 7.50–7.46 (4H, m), 7.40–7.37 (6H, m), 7.06 (1H, s), 2.58 (3H, d, J = 0.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.19 (d, J = 3.8 Hz), 148.32 (d, J = 15.3 Hz), 143.42 (d, J = 2.8 Hz), 136.40 (d, J = 11.4 Hz), 134.11 (d, J = 19.4 Hz), 130.24, 129.17, 128.86, 128.48 (d, J = 7.0 Hz), 126.88, 126.53, 124.88 (d, J = 14.6 Hz), 123.60, 18.71; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –2.45; *m/z* HRMS (DART) found $[M+H]^+$ 328.1254, $C_{22}H_{19}NP^+$ requires 328.1255.

2-(Diphenylphosphaneyl)-4-ethoxyquinoline (2g)



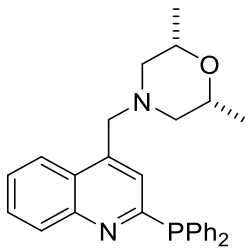
Prepared according to general procedure A, using 4-ethoxyquinoline (500 mg, 3.00 mmol), Tf_2O (500 μL, 3.00 mmol), methyl-3-(diphenylphosphaneyl)propanoate (900 mg, 3.30 mmol), DBU (1.35 mL, 9.00 mmol), and CH_2Cl_2 (60 mL). The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a white crystalline solid (880 mg, 2.46 mmol, 82% yield). mp 114-118 ºC; IR ν_{max}/cm^{-1} (film): 3058, 2975, 1482, 1231, 1115, 1018, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (1H, dd, J = 8.8, 1.2 Hz), 8.05 (1H, d, J = 8.2 Hz), 7.70-7.64 (1H, m), 7.51-7.39 (5H, m); 7.38-7.31 (6H, m), 6.49 (1H, d, J = 0.6 Hz), 3.94 (2H, q, J = 7.0 Hz), 1.41 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.60 (d, J = 4.7 Hz), 160.96 (d, J = 3.5 Hz), 149.60 (d, J = 16.9 Hz), 136.56 (d, J = 11.9 Hz), 134.10 (d, J = 19.4 Hz), 129.73, 129.15, 128.92, 128.49 (d, J = 7.0 Hz), 125.72, 121,72, 120.23, 104.02, 63.69, 14.22 ^{31}P NMR (162 MHz, $CDCl_3$) δ: –1.06; *m/z* HRMS (DART) found $[M+H]^+$ 358.1349 $C_{23}H_{21}N_2OP^+$ requires 358.1355.

Ethyl (*S*)-4-((4-chlorophenyl)(4-(diphenylphosphaneyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate (2h)



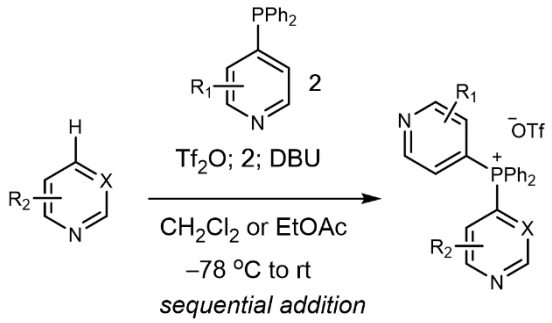
Prepared according to general procedure A using ethyl (*S*)-4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (1.026 g, 2.74 mmol), Tf_2O (0.46 mL, 2.74 mmol), methyl 3-(diphenylphosphaneyl)propanoate (820 mg, 3.01 mmol), DBU (1.22 mL, 8.21 mmol) and CH_2Cl_2 (27.5 mL). Flash column chromatography (silica gel, gradient elution: 45% EtOAc in hexanes to 50% EtOAc in hexanes) afforded the title compound as a tan oil (1.19 g, 2.13 mmol, 78% yield). IR ν_{max}/cm^{-1} (film): 3052, 2981, 2928, 1692, 1577, 1489, 1434, 1381, 1272, 1227, 1087, 742; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.37 (1H, ddd, *J* = 5.1, 2.3, 0.8 Hz), 7.41-7.19 (15H, m), 6.95 (1H, m), 5.52 (1H, s), 4.10 (2H, q, *J* = 7.2 Hz), 3.61-3.45 (3H, m), 3.25-3.06 (2H, m), 1.80-1.67 (1H, m), 1.63-1.38 (3H, m), 1.23 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.03 (d, *J* = 4.2 Hz), 155.36, 150.31 (d, *J* = 18.2 Hz), 148.31 (d, *J* = 4.2 Hz), 139.82, 134.79 (d, *J* = 10.1 Hz), 134.76 (d, *J* = 10.1 Hz), 134.12 (d, *J* = 20.7 Hz), 134.01 (d, *J* = 20.7 Hz), 133.31, 129.51 (d, *J* = 2.8 Hz), 128.72 (d, *J* = 7.6 Hz), 128.45, 128.14, 125.75 (d, *J* = 15.0 Hz), 123.83 (d, *J* = 15.6 Hz), 80.72, 72.23, 61.13, 40.69, 30.80, 30.66, 14.64; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –6.35; *m/z* HRMS (DART) found $[M+H]^+$ 559.1947, $C_{32}H_{33}ClN_2O_3P^+$ requires 559.1917.

(*2R, 6S*)-4-((2-(Diphenylphosphaneyl)quinolin-4-yl)methyl)-2,6-dimethylmorpholine (2i)



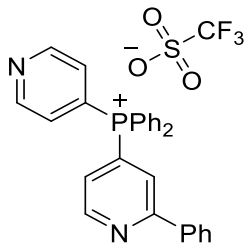
Prepared according to general procedure A, using (*2R, 6S*)-2,6-dimethyl-4-(quinolin-4-ylmethyl)morpholine (1.28 g, 5.00 mmol), Tf_2O (840 μL, 5.00 mmol), methyl-3-(diphenylphosphaneyl)propanoate (1.50 g, 5.50 mmol), DBU (2.25 mL, 15.00 mmol), and CH_2Cl_2 (50 mL). Crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a white amorphous solid (1.42 g, 3.25 mmol, 65% yield). IR ν_{max}/cm^{-1} (film): 3054, 2971, 2932, 2868, 2811, 2236, 570, 566, 542, 537, 529; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.95 (1H, d, *J* = 8.5 Hz), 7.88 (1H, d, *J* = 8.0 Hz), 7.48 (1H, m), 7.33 (1H, m), 7.30-7.24 (4H, m), 7.20-7.12 (6H, m), 7.07 (1H, s), 3.59 (2H, s), 3.35-3.24 (2H, m), 2.37 (2H, d, *J* = 10.4 Hz), 1.57 (2H, t, *J* = 10.7 Hz), 0.90 (6H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164. 39 (d, *J* = 3.7 Hz), 148.59 (d, *J* = 15.1 Hz), 142.58 (d, *J* = 2.7 Hz), 136.39 (d, *J* = 11.3 Hz), 134.05 (d, *J* = 19.5 Hz) 130.26, 129.12, 128.90, 128.45 (d, *J* = 6.9 Hz), 126.5, 125.96, 123.94 (d, *J* = 14.5 Hz), 123.45, 71.46, 59.42, 58.82, 18.94; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –2.22; *m/z* HRMS (DART) found $[M+H]^+$ 441.2065, $C_{28}H_{30}N_2OP^+$ requires 441.2090.

A 2.3.3 General Procedure B (Preparation of Heteroaryl Phosphonium Salts)



An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before the mixture was warmed to –50 ºC and then the heteroaryl phosphine (1.1 equiv) was added in one portion as a solid or dropwise as a solution (2.0 M in CH_2Cl_2). The reaction was subjected to three rapid cycles of vacuum / nitrogen backfill and was stirred for a further 30 minutes at –50 ºC. The reaction was cooled to –78 ºC and DBU (1.0 equiv) was added dropwise via syringe, the cooling bath was removed, and the reaction was allowed to warm to room temperature while stirring (approximately 15-30 minutes). The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O (3x). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to approximately 2-10 mL (depending on the scale of the reaction). The concentrated reaction mixture was added dropwise to an excess of chilled Et_2O (0 ºC) that was then placed in a –20 ºC refrigerator for approximately 2-12 hours. The suspension was filtered on a frit, the solid washed with chilled Et_2O (0 ºC) and dried *in vacuo* to provide the pure phosphonium salt.

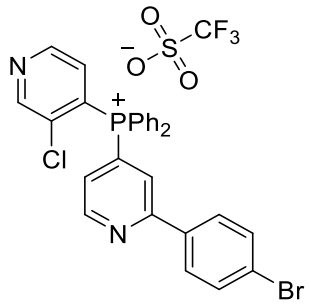
Diphenyl(2-phenylpyridin-4-yl)(pyridin-4-yl)phosphonium trifluoromethanesulfonate (3a)



Prepared according to general procedure B using pyridine (119 μL, 1.50 mmol), Tf_2O (250 μL, 1.50 mmol), 4-(diphenylphosphaneyl)-2-phenylpyridine (560 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol) and CH_2Cl_2 (15 mL). After the purification procedure

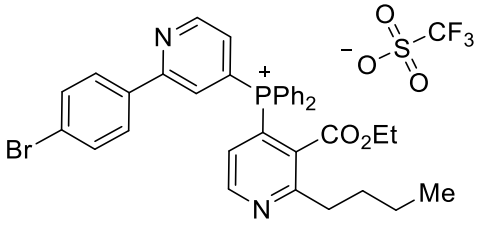
(solid was dissolved in approximately 2-10 mL of CH_2Cl_2 and the solution was again added dropwise to an excess of chilled Et_2O (0 °C). The mixture was then placed in −20 °C refrigerator for 5 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled Et_2O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt), the title compound was isolated as a white solid (702 mg, 1.24 mmol, 83% yield). mp 73 ºC; IR ν_{max}/cm^{-1} (film): 3059, 1573, 1440, 1262, 1223, 1150, 1109, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.09 (1H, app t, *J* = 5.1 Hz), 9.03 (2H, app t, *J* = 5.1 Hz), 7.99-7.87 (4H, m) 7.87-7.78 (5H, m), 7.77-7.63 (6H, m), 7.57 (1H, dd, *J* = 13.1, 5.1 Hz), 7.48-7.41 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.99 (d, *J* = 10.4 Hz), 151.60 (d, *J* = 11.8 Hz), 151.49 (d, *J* = 10.3 Hz), 136.49 (d, *J* = 1.6 Hz), 136.35 (d, *J* = 3.0 Hz), 134.29 (d, *J* = 10.7 Hz), 130.93 (d, *J* = 13.3 Hz), 130.14, 128.75, 127.40 (d, *J* = 84.4 Hz), 126.98 (d, *J* = 8.2 Hz), 126.89, 126.39 (d, *J* = 84.3 Hz), 125.18 (d, *J* = 8.3 Hz), 122.96 (d, *J* = 8.9 Hz), 120.38 (q, *J* = 321.4 Hz), 113.59 (d, *J* = 89.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: −78.14; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.76; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 417.1537, $C_{28}H_{22}N_2P^+$ requires 417.1521.

(2-(4-Bromophenyl)pyridin-4-yl)(3-chloropyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (3b)



Prepared according to general procedure B using 3-chloropyridine (95 μL, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 2-(4-Bromophenyl)-4-(diphenylphosphaneyl)pyridine (460 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After the purification procedure, the title compound was isolated as a white solid (556 mg, 0.82 mmol, 82% yield). mp 94-96 ºC; IR ν_{max}/cm^{-1} (film): 3062, 1579, 1439, 1258, 1223, 1149, 1107, 1029, 724; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.04 (1H, app t, *J* = 5.4 Hz), 8.97-8.82 (2H, m), 8.02 (1H, d, *J* = 14.5 Hz), 7.96-7.85 (4H, m), 7.84-7.72 (8H, m), 7.64-7.52 (3H, m), 7.41 (1H, dd, *J* = 15.1, 5.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.30 (d, *J* = 10.8 Hz), 151.78 (d, *J* = 11.1 Hz), 151.59 (d, *J* = 5.1 Hz), 150.33 (d, *J* = 10.1 Hz), 136.46 (d, *J* = 3.0 Hz), 135.67 (d, *J* = 1.7 Hz), 134.51, 134.27, 132.14, 131.17 (d, *J* = 13.6 Hz), 130.91 (d, *J* = 8.4 Hz), 128.93, 127.66 (d, *J* = 85.7 Hz), 125.57 (d, *J* = 88.3 Hz), 125.33 (d, *J* = 8.5 Hz), 125.13, 123.02 (d, *J* = 9.1 Hz), 120.57 (q, *J* = 321.2 Hz), 113.39 (d, *J* = 90.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.18; ^{31}P (162 MHz, $CDCl_3$) δ: 22.17; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 529.0239, $C_{28}H_{20}BrClN_2P^+$ requires 529.0236.

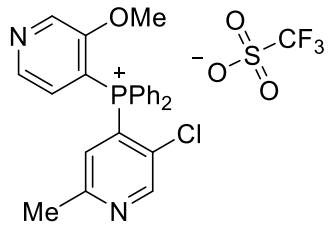
(2-(4-Bromophenyl)pyridin-4-yl)(2-butyl-3-(ethoxycarbonyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (3c)



Prepared according to general procedure B (except that after 2-(4-bromophenyl)-4-(diphenylphosphino)pyridine was added, the reaction mixture was stirred for 30 min at -30 °C) using ethyl 2-butylnicotinate (300.4 mg, 1.45 mmol), Tf_2O (244 μL, 1.45 mmol), 2-(4-bromophenyl)-4-(diphenylphosphino)pyridine (667 mg, 1.60 mmol), DBU (218 μL, 1.45 mmol) and CH_2Cl_2 (14.5 mL). After the purification procedure, the title compound was isolated as a white amorphous powder (831 mg, 1.07 mmol, 74% yield). mp 212-214 °C; IR υ_{max}/cm^{-1} (film): 3045, 2950, 2927, 2870, 1706, 1787, 1578, 1547, 1538, 1463, 1440, 1435, 1404, 1369, 1291, 1275, 1258, 1223, 1177, 1152, 1136, 1105, 1069, 1030, 1013, 1004, 816, 751, 727, 721, 697, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.04-9.00 (2H, m), 7.94-7.84 (5H, m), 7.80-7.69 (8H, m), 7.60-7.54 (3H, m), 7.33 (1H, dd, *J* = 15.7, 5.0 Hz), 3.51 (2H, q, *J* = 7.2 Hz), 3.07 (2H, t, *J* = 7.8 Hz), 1.82-1.74 (2H, m), 1.41 (2H, sext, *J* = 7.4 Hz), 0.99-0.93 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.34 (d, *J* = 3.7 Hz), 164.12 (d, *J* = 6.3 Hz), 157.79 (d, *J* = 10.6 Hz), 153.20 (d, *J* = 11.6 Hz), 151.37 (d, *J* = 11.0 Hz), 135.91 (d, *J* = 2.9 Hz), 135.84 (d, *J* = 1.7 Hz), 134.53 (d, *J* = 10.5 Hz), 132.17, 130.65 (d, *J* = 13.3 Hz), 129.71 (d, *J* = 86.4 Hz), 128.79, 128.50 (d, *J* = 4.9 Hz), 127.95 (d, *J* = 9.5 Hz), 126.79 (d, *J* = 83.3 Hz), 125.40 (d, *J* = 8.1 Hz), 125.07, 123.09 (d, *J* = 8.8 Hz), 120.66 (q, *J* = 319.6 Hz), 115.84 (d, *J* = 90.5 Hz), 63.18, 37.27 (d, *J* = 1.5 Hz), 31.87, 22.62, 13.75, 13.26; ^{19}F

NMR (365 MHz, $CDCl_3$) δ: –78.19; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 27.28; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 623.1460, $C_{35}H_{33}BrN_2O_2P^+$ requires 623.1463.

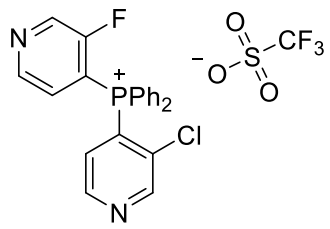
(5-Chloro-2-methylpyridin-4-yl)(3-methoxypyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (3d)



Prepared according to general procedure B (except that after 5-chloro-4-(diphenylphosphino)-2-methylpyridine was added, the reaction mixture was stirred for 30 min at –30 °C) using 3-methoxypyridine (202 μL, 2.00 mmol), Tf_2O (336 μL, 2.00 mmol), 5-chloro-4-(diphenylphosphino)-2-methylpyridine (686 mg, 2.20 mmol), DBU (300 μL, 2.00 mmol) and CH_2Cl_2 (20 mL). After the purification procedure, the title compound was isolated as an amorphous white powder (842 mg, 1.48 mmol, 74% yield). mp 182-186 °C; IR υ_{max}/cm^{-1} (film): 3060, 2951, 1570, 1544, 1483, 1460, 1439, 1411, 1380, 1326, 1300, 1258, 1222, 1140, 1103, 1087, 1072, 1043, 1029, 998, 914, 823, 808, 753, 722, 688, 646; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.74 (1H, d, J = 6.6 Hz), 8.70 (1H, d, J = 6.7 Hz), 8.62 (1H, t, J = 4.6 Hz), 7.91-7.87 (2H, m), 7.81-7.76 (4H, m), 7.72-7.67 (4H, m), 7.39 (1H, dd, J = 15.2, 5.0 Hz), 7.26 (1H, d, J = 15.6 Hz), 3.72 (3H, s), 2.65 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.05 (d, J = 10.2 Hz), 155.60, 150.83 (d, J = 5.7 Hz), 144.17 (d, J = 11.3 Hz), 136.64 (d, J = 4.5 Hz), 135.91 (d, J = 3.1 Hz), 134.11 (d, J = 11.2 Hz), 130.81 (d, J = 13.7 Hz), 130.79 (d, J = 2.2 Hz), 129.12 (d, J = 8.1 Hz), 127.68 (d, J = 6.8 Hz), 126.35 (d, J = 90.1 Hz), 120.68 (q, J = 319.6 Hz), 114.06 (d, J = 92.0 Hz), 113.45 (d, J = 88.4 Hz), 57.39 (dd, J = 4.6, 5.9 Hz), 24.19; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.26; ^{31}P NMR (162 MHz,

$CDCl_3$) δ: 21.15; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 419.1099, $C_{24}H_{21}ClN_2OP^+$ requires 419.1080.

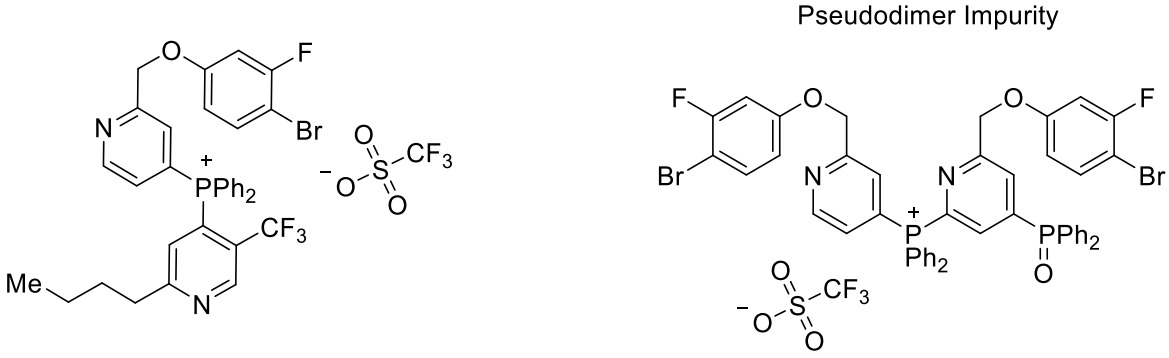
(3-Chloro-pyridin-4-yl)(3-fluoropyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (3e)



Prepared according to general procedure B (except that after the initial extraction the aqueous layer was extracted an additional 3 times with CH_2Cl_2 and then the combined organic was washed once with water prior to concentration) using 3-fluoropyridine (43 μL, 0.50 mmol), Tf_2O (84 μL, 0.50 mmol), 3-chloro-4-(diphenylphosphino)pyridine (164 mg, 0.55 mmol), DBU (75 μL, 0.50 mmol) and CH_2Cl_2 (5.0 mL). After the purification procedure (concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of 50% Et_2O in hexanes instead of Et_2O), the title compound was isolated as a pale yellow solid (148 mg, 0.27 mmol, 54% yield). mp 59-62 °C; IR υ_{max}/cm^{-1} (film): 3085, 3024, 1586, 1546, 1472, 1440, 1403, 1282, 1247, 1225, 1201, 1184, 1154, 1132, 1106, 1030, 996, 749; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.99-8.71 (4H, m), 8.02-7.68 (2H, m), 7.83-7.57 (9H, m), 7.45 (1H, dd, *J* = 15.4, 4.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 160.39 (d, *J* = 264.3Hz), 153.28 (d, *J* = 5.2 Hz), 151.07 (d, *J* = 10.4 Hz), 149.09 (dd, *J* = 10.7, 5.3 Hz), 141.83 (dd, *J* = 24.0, 4.1 Hz), 137.73 (d, *J* = 3.2 Hz), 136.19 (d, *J* = 2.0 Hz), 135.86 (d, *J* = 11.7 Hz), 132.22 (d, *J* = 14.1 Hz), 131.34 (d, *J* = 8.7 Hz), 129.60 (d, *J* = 3.8 Hz), 127.07 (d, *J* = 91.3 Hz), 121.73 (d, *J* = 319.0 Hz), 116.20 (dd, *J* = 87.5, 13.3 Hz), 115.76 (d, *J* = 13.3 Hz); ^{19}F NMR (365

MHz, CD_3OD) δ: −79.79, −111.00; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.61 (d, *J* = 4.0 Hz); *m/z* LRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 393.1, $C_{22}H_{16}ClFN_2OP^+$ requires 393.1.

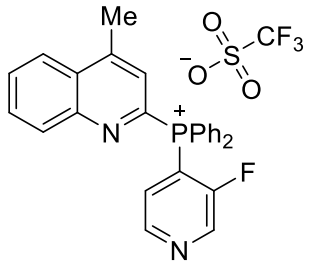
(2-((4-Bromo-3-fluorophenoxy)methyl)pyridin-4-yl)(2-butyl-5-(trifluoromethyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate and (6-((4-bromo-3-fluorophenoxy)methyl)-4-(diphenylphosphoryl)pyridin-2-yl)(2-((4-bromo-3-fluorophenoxy)methyl)pyridin-4-yl)diphenylphosphonium (3f)



Prepared according to general procedure B using 2-butyl-5-(trifluoromethyl)pyridine (93 mg, 0.46 mmol), Tf_2O (77 μL, 0.46 mmol), 2-((4-bromo-3-fluorophenoxy)methyl)-4-(diphenylphosphino)pyridine (234 mg, 0.50 mmol), DBU (68 μL, 0.46 mmol) and CH_2Cl_2 (4.6 mL). After the purification procedure, the title compounds were isolated as a mixture (crude: 3.7:1; pure: 5.6:1) as a white amorphous powder (204 mg). The mixture was carried forward through the ligand coupling step. IR υ_{max}/cm^{-1} (film): 3063, 2959, 2932, 2872, 1603, 1578, 1532, 1486, 1439, 1384, 1320, 1259, 1223, 1143, 1120, 1106, 1029, 997, 968, 945, 909, 848, 834, 727; Major, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.16 (1H, d, *J* = 7.3 Hz), 9.03 (1H, t, *J* = 5.2 Hz), 7.93-7.90 (2H, m), 7.80-7.62 (10H, m), 7.36 (1H, t, *J* = 8.4 Hz), 7.21 (1H, d, *J* = 17.4 Hz), 6.63 (1H, dd, *J* = 10.0, 2.7 Hz), 6.58 (1H, dd, *J* = 8.7, 2.4 Hz), 5.33 (2H, s), 2.94 (2H, t, *J* = 7.7 Hz), 1.66 (2H, qn, *J* = 7.6

Hz), 1.31 (2H, sext, J = 7.5 Hz), 0.87 (3H, t, J = 7.3 Hz); Major, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.37 (d, J = 9.8 Hz), 159.21 (d, J = 245.9 Hz), 158.88 (d, J = 10.3 Hz), 157.97 (d, J = 9.8 Hz), 151.53 (d, J = 10.7 Hz), 150.06 (m), 136.40 (d, J = 3.0 Hz), 134.56 (d, J = 7.7 Hz), 133.52, 130.93 (d, J = 13.4 Hz), 130.24 (d, J = 8.5 Hz), 128.43 (d, J = 84.9 Hz), 126.52 (d, J = 8.5 Hz), 124.46 (d, J = 8.8 Hz), 124.17 (d, J = 4.1 Hz), 123.82 (d, J = 79.6 Hz), 122.48 (qd, J = 273.8, 2.3 Hz), 120.56 (q, J = 319.5 Hz), 114.65 (d, J = 89.3 Hz), 111.81 (d, J = 3.0 Hz), 103.90 (d, J = 25.5 Hz), 100.22 (d, J = 21.1 Hz), 70.00 (d, J = 1.5 Hz), 37.94, 30.25, 22.14, 13.63; Major, ^{19}F NMR (365 MHz, $CDCl_3$) δ: −53.41 (d, J = 1.7 Hz), −78.35, −104.68 (t, J = 8.4 Hz); Major, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 26.97 (d, J = 2.4 Hz); *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 667.1166, $C_{34}H_{29}BrF_4N_2OP^+$ requires 667.1137.

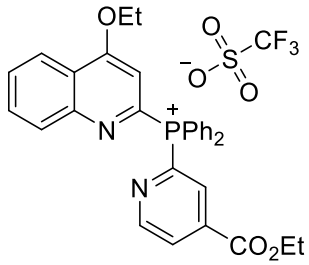
(3-Fluoropyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (3g)



Prepared according to general procedure B, using 3-fluoropyridine (171 μL, 2.00 mmol), Tf_2O (336 μL, 2.00 mmol), 2-(diphenylphosphaneyl)-4-methylquinoline (720 mg, 2.20 mmol), DBU (300 μL, 2.00 mmol), and CH_2Cl_2 (20 mL). After purification procedure, the title compound was provided as a light brown crystalline solid (660 mg, 1.16 mmol, 58% yield). mp 65-66 °C IR ν_{max}/cm^{-1} (film): 3064, 1545, 1505, 997, 857, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88-8.83 (2H, m), 8.19 (1H, d, J = 8.2 Hz), 8.14 (1H, d, J = 8.2 Hz), 7.95-7.78 (13H, m), 7.41 (1H, dt, J = 14.2,

5.1 Hz), 2.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.98 (d, *J* = 265.8 Hz), 149.37 (d, *J* = 11.4 Hz), 148.49 (d, *J* = 23.9 Hz), 148.15 (dd, *J* = 9.9, 6.4 Hz), 142.67 (d, *J* = 120.2 Hz), 139.85 (dd, *J* = 22.9, 3.8 Hz), 136.27 (d, *J* = 31.1 Hz), 134.67 (d, *J* = 10.6 Hz), 131.68, 130.92 (d, *J* = 13.4 Hz), 130.65 (d, *J* = 1.2 Hz), 130.54, 129.45 (d, *J* = 3.1 Hz), 128.86 (dd, *J* = 7.0, 1.7 Hz), 125.22 (d, *J* = 27.1 Hz), 124.61 (d, *J* = 1.4 Hz), 120.79 (q, *J* = 321.1 Hz), 116.43 (dd, *J* = 84.7, 13.9 Hz), 114.84 (d, *J* = 88.9 Hz), 19.19 (d, *J* = 1.6 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.25, –109.74 (d, *J* = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 11.79; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 423.1454, $C_{27}H_{21}FN_2P^+$ requires 423.1426.

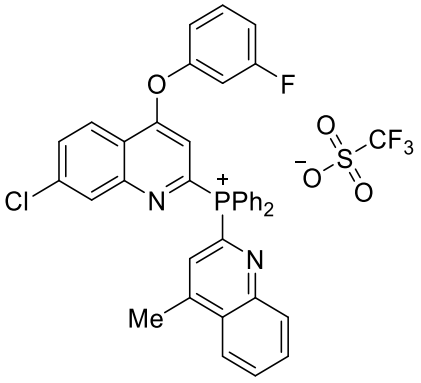
(4-(Ethoxycarbonyl)pyridin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (3h)



Prepared according to general procedure B, using 4- picolyl acid ethyl ester (150 μL, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 2-(diphenylphosphaneyl)-4-ethoxyquinoline (392 mg, 1.10 mmol), DBU (150 μL, 1.00 mmol), and CH_2Cl_2 (10 mL). After purification procedure,

(concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of 50% Et_2O in hexanes instead of Et_2O) the title compound was provided as a light brown amorphous solid (400 mg, 0.61 mmol, 61% yield). IR ν_{max}/cm^{-1} (film): 3064, 2986, 1729, 1476, 942, 851, 557, 537; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.19 (1H, d, *J* = 4.8 Hz), 8.48 (1H, d, *J* = 5.8 Hz), 8.35 (1H, d, *J* = 8.3 Hz), 8.31-8.25 (1H, m), 8.05 (1H, d, *J* = 8.5 Hz), 7.93-7.66 (12H, m), 7.18 (1H, d, *J* = 6.2 Hz), 4.40 (2H, q, *J* = 7.1 Hz), 4.22 (2H, q, *J* = 7.0 Hz), 1.51 (3H, t, *J* = 7.0 Hz), 1.35 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.46 (d, *J* = 14.2 Hz), 163.15 (d, *J* = 2.7 Hz), 153.32 (d, *J* = 20.0 Hz), 149.59 (d, *J* = 25.9 Hz), 145.87 (d, *J* = 120.4 Hz), 145.13 (d, *J* = 119.0 Hz), 139.52 (d, *J* = 10.4 Hz), 135.75 (d, *J* = 3.1 Hz), 134.91 (d, *J* = 9.9 Hz), 131.83, 131.26 (d, *J* = 24.2 Hz), 130.45 (d, *J* = 13.0 Hz), 129.31 (d, *J* = 18.0 Hz), 127.48 (d, *J* = 3.5 Hz), 122.66, 121.93 (d, *J* = 2.5 Hz), 120.78 (q, *J* = 321.0 Hz), 116.87 (d, *J* = 87.9 Hz), 106.06, 105.78, 65.83, 62.74, 14.04, 13.92; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.25; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 9.58; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 507.1919, $C_{31}H_{28}N_2O_3P^+$ requires 507.1832.

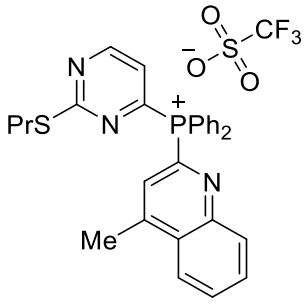
(7-Chloro-4-(3-fluorophenoxy)quinolin-2-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (3i)



Prepared according to general procedure B, using 7-chloro-4-(3-fluorophenoxy)quinoline (244 mg, 0.89 mmol), Tf_2O (151 μL, 0.89 mmol), 2-(diphenylphosphaneyl)-4-methylquinoline

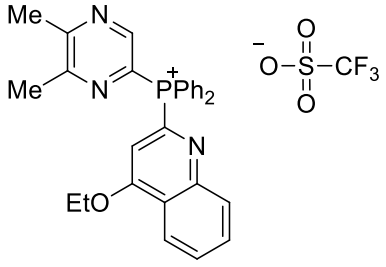
(320 mg, 0.99 mmol), DBU (133 μL, 0.89 mmol), and CH_2Cl_2 (9 mL). After purification procedure, the title compound was provided as a brown amorphous solid (330 mg, 0.47 mmol, 53% yield). IR ν_{max}/cm^{-1} (film): 3067, 1607, 666, 605, 579, 544, 532; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.41 (1H, d, *J* = 9.0 Hz), 8.16-8.14 (2H, m), 7.92-7.67 (15H, m), 7.54 (1H, d, *J* = 4.6 Hz), 7.31 (1H, q, *J* = 5.8 Hz), 7.10 (1H, d, *J* = 5.6 Hz), 6.98 (1H, dd, *J* = 8.2, 1.8 Hz), 6.92-6.84 (2H, m), 2.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.16 (d, *J* = 249.9 Hz), 162.90 (d, *J* = 13.9 Hz), 153.49 (d, *J* = 10.4 Hz), 150.56 (d, *J* = 25.7 Hz), 148.76 (d, *J* = 10.6 Hz), 148.15 (d, *J* = 8.6 Hz), 147.67 (d, *J* = 132.3 Hz), 143.40 (d, *J* = 114.9 Hz), 138.65, 135.63 (d, *J* = 3.1 Hz), 134.76 (d, *J* = 9.8 Hz), 131.75 (d, *J* = 9.4 Hz), 131.56, 130.77, 130.66, 130.35 (d, *J* = 12.9 Hz), 128.87 (d, *J* = 3.0 Hz), 128.57 (d, *J* = 1.0 Hz), 128.56, 126.04 (d, *J* = 25.7 Hz), 124.47 (d, *J* = 1.3 Hz), 123.78, 120.77 (q, *J* = 321.2 Hz), 119.87 (d, *J* = 2.5 Hz), 116.91 (d, *J* = 87.7 Hz), 117.03 (d, *J* = 3.5 Hz), 113.69 (d, *J* = 20.9 Hz), 109.23 (d, *J* = 27.4 Hz), 108.87 (d, *J* = 24.2 Hz), 19.14 (d, *J* = 1.5 Hz) ; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.19, –108.64 (q, *J* = 8.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 8.06; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 599.1450, $C_{38}H_{27}ClFN_2OP^+$ requires 599.1467.

(4-Methylquinolin-2-yl)diphenyl(2-(propylthio)pyrimidin-4-yl)phosphonium trifluoromethanesulfonate (3j)



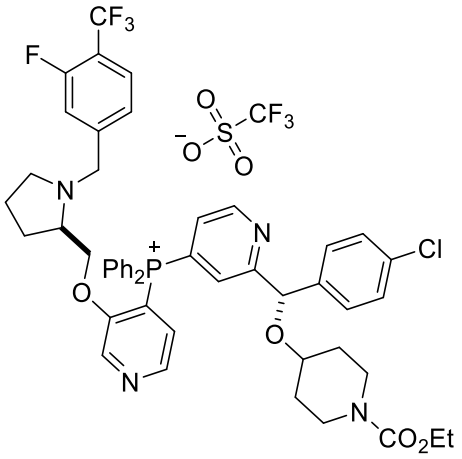
Prepared according to general procedure B (except the stirring time after the addition of the heteroaryl phosphine was 45 minutes instead of 30 minutes) using 2-(propylthio)pyrimidine (154 mg, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 2-(diphenylphosphaneyl)-4-methylquinoline (360 mg, 1.10 mmol), DBU (149, 1.00 mmol) and EtOAc (5 mL). After the purification procedure, the title compound was isolated as a brown solid (433 mg, 0.72 mmol, 72% yield). mp 52-54 ºC; IR ν_{max}/cm^{-1} (film): 3064, 2963, 1576, 1544, 1526, 1439, 1259, 1143, 1029, 727; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.91 (1H, dd, *J* = 7.6, 4.8 Hz), 8.21-8.12 (2H, m), 7.95-7.87 (3H, m), 7.87-7.80 (5H, m), 7.80-7.73 (4H, m), 7.70 (1H, dd, *J* = 6.0, 4.8 Hz), 7.65 (1H, d, *J* = 4.8 Hz), 2.93 (2H, t, *J* = 7.3 Hz), 2.83 (3H, s), 1.53 (2H, sext, *J* = 7.3 Hz), 0.84 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.98 (d, *J* = 18.0 Hz), 159.91 (d, *J* = 7.3 Hz), 154.41 (d, *J* = 111.9 Hz), 148.87 (d, *J* = 10.7 Hz), 148.51 (d, *J* = 23.4 Hz), 142.36 (d, *J* = 117.1 Hz), 136.04 (d, *J* = 3.0 Hz), 134.99 (d, *J* = 9.9 Hz), 131.72, 130.77-130.43 (3C, m), 129.12 (d, *J* = 3.0 Hz), 125.98 (d, *J* = 26.5 Hz), 124.51 (d, *J* = 1.2 Hz), 123.11 (d, *J* = 19.6 Hz), 120.74 (q, *J* = 321.1 Hz), 115.21 (d, *J* = 87.3 Hz), 33.05, 22.02, 19.18 (d, *J* = 1.5 Hz), 13.23; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.21; ^{31}P (162 MHz, $CDCl_3$) δ: 9.49; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 480.1673, $C_{29}H_{27}N_3PS^+$ requires 480.1663.

(5,6-Dimethylpyrazin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (3k)



Prepared according to general procedure B using 2,3-dimethylpyrazine (128 μL, 1.20 mmol), Tf_2O (336 μL, 1.20 mmol), 2-(diphenylphosphino)-4-ethoxyquinoline (472 mg, 1.32 mmol), DBU (180 μL, 1.20 mmol) and CH_2Cl_2 (12 mL). After the purification procedure (concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of hexanes instead of Et_2O and placed at room temperature overnight), the title compound was isolated as a light brown amorphous powder (663 mg, 1.08 mmol, 90% yield). mp 145-148 °C; IR υ_{max}/cm^{-1} (film): 3066, 2989, 1571, 1551, 1507, 1438, 1410, 1385, 1354, 1316, 1260, 1222, 1192, 1145, 1108, 1029, 997, 771, 751, 728, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (1H, s), 8.35 (1H, d, *J* = 8.4 Hz), 8.04 (1H, d, *J* = 8.5 Hz), 7.90-7.81 (7H, m), 7.77-7.70 (5H, m), 7.26 (1H, d, *J* = 6.1 Hz), 4.25 (2H, q, *J* = 7.0 Hz), 2.73 (3H, s), 2.69 (3H, s), 1.52 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.27 (d, *J* = 14.0 Hz), 159.36 (d, *J* = 3.4 Hz), 156.13 (d, *J* = 15.5 Hz), 149.50 (d, *J* = 25.9 Hz), 147.83 (d, *J* = 23.3 Hz), 144.83 (d, *J* = 118.6 Hz), 136.09 (d, *J* = 83.7 Hz), 135.67 (d, *J* = 3.0 Hz), 134.74 (d, *J* = 9.9 Hz), 131.76, 130.37 (d, *J* = 12.9 Hz), 129.38, 129.16, 122.50, 121.80 (d, *J* = 2.4 Hz), 120.73 (q, *J* = 319.6 Hz), 116.49 (d, *J* = 87.7 Hz), 105.64 (d, *J* = 29.0 Hz), 65.66, 22.76, 22.42, 14.01; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.26; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 7.50; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 464.1931, $C_{29}H_{27}N_3OP^+$ requires 464.1892.

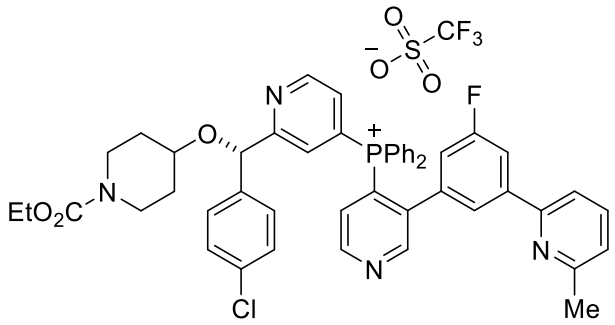
(2-((*S*)-(4-Chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)(3-(((*R*)-1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (3l)



Prepared according to general procedure B, using (*R*)-3-((1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridine (177 mg, 0.50 mmol), Tf_2O (85 μL, 0.50 mmol), ethyl (*S*)-4-((4-chlorophenyl)(4-(diphenylphosphaneyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate (307 mg, 0.55 mmol), DBU (75 μL, 0.89 mmol), and CH_2Cl_2 (5 mL). After the purification procedure (concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of 50% Et_2O in hexanes instead of Et_2O), the title compound was provided as a brown amorphous solid (370 mg, 0.35 mmol, 70% yield). IR ν_{max}/cm^{-1} (film): 3061, 2950, 2873, 825, 560, 557, 535, 528; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.90 (1H, t, *J* = 5.1 Hz), 8.74 (1H, d, *J* = 6.4 Hz), 8.57 (1H, t, *J* = 4.4 Hz), 7.92-7.45 (13H, m), 7.36-7.27 (4H, m), 7.14-6.96 (3H, m), 5.72 (1H, s), 4.21-4.04 (3H, m), 3.89-3.78 (1H, m), 3.69-3.44 (4H, m), 3.32-3.05 (3H, m), 2.85-2.65 (1H, m), 2.24-1.94 (2H, br), 1.83-1.63 (3H, m), 1.48-1.35 (4H, m), 1.34-1.16 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.41 (d, *J* = 9.9 Hz), 159.67 (dq, *J* = 256.0, 2.4 Hz), 155.43, 155.18, 151.30 (d, *J* = 10.5 Hz), 144.50 (d, *J* = 11.4 Hz), 138.69, 136.28-136.10 (m), 134.25-134.02 (m, 2C), 132.57, 131.94 (dd, *J* = 14.6, 4.6 Hz), 131.03 (dd, *J* = 13.4, 7.7 Hz), 128.89, 128.86 (d, *J* = 15.3 Hz), 128.69 (d, *J* = 4.8 Hz), 128.59 (d, *J* = 85.2 Hz), 128.52 (d, *J* = 70.8 Hz), 128.32, 127.31-127.08 (m), 125.56 (d, *J* = 8.6 Hz), 123.15 (d, *J* = 9.4 Hz), 122.51 (dq, *J* = 271.8, 1.9 Hz), 120.63

(q, J = 320.7 Hz), 114.79 (dd, J = 81.0, 28.2 Hz), 113.05 (d, J = 88.0 Hz), 72.56, 61.37, 57.85, 54.02, 53.99, 40.82, 40.76, 31.46, 30.43, 29.67, 27.89, 22.63, 14.66; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –61.18 (d, J = 13.2 Hz), –78.25, –113.33-115.80 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.01; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 911.3094, $C_{50}H_{49}ClF_4N_4O_4P^+$ requires 911.3116.

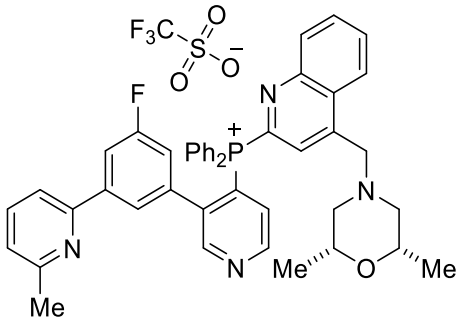
(*S*)-(2-((4-Chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)(3-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (3m)



Prepared according to general procedure B using 2-(3-fluoro-5-(pyridin-3-yl)phenyl)-6-methylpyridine (132 mg, 0.50 mmol), Tf_2O (84 μL, 0.50 mmol), ethyl (S)-4-((4-chlorophenyl)(4-(diphenylphosphaneyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate (308 mg, 0.55 mmol), DBU (75 μL, 0.50 mmol) and CH_2Cl_2 (5 mL). After the purification procedure, the title compound was isolated as a white solid (305 mg, 0.31 mmol, 63% yield). mp 103-109 ºC; IR ν_{max}/cm^{-1} (film): 3063, 2928, 1687, 1438, 1261, 1224, 1149, 1030, 796; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00 (1H, app t, J = 4.7 Hz), 8.82 (1H, d, J = 7.0 Hz), 8.74 (1H, app t, J = 5.3 Hz), 7.81-7.72 (2H, m), 7.71-7.60 (9H, m), 7.58-7.47 (3H, m), 7.44 (1H, d, J = 9.8 Hz), 7.28 (1H, s), 7.29-7.19 (6H, m), 7.07 (1H, d, J = 7.6 Hz), 7.02 (1H, d, J = 7.7 Hz), 6.46 (1H, d, J = 8.3 Hz) 5.62 (1H, s), 4.09 (2H, q, J = 7.2 Hz), 3.62-3.44 (3H, m), 3.17-3.02 (2H, m), 2.44 (3H, s), 1.73-1.59 (2H, m), 1.48-1.33 (2H, m), 1.23 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.84 (d, J = 9.9 Hz), 162.21 (d, J

= 249.4 Hz), 158.45, 155.36, 153.28 (d, *J* = 7.8 Hz), 152.76 (d, *J* = 2.2 Hz), 150.98-150.64 (2C, m), 141.63 (d, *J* = 7.8 Hz), 140.06 (d, *J* = 7.2 Hz), 138.47, 137.34, 136.68-136.51 (m), 136.01-135.82 (m), 134.63-134.36 (m), 133.90, 130.80 (d, *J* =13.3 Hz), 128.74 (d, *J* = 83.4 Hz), 128.72, 128.62 (d, *J* = 9.0 Hz), 128.43, 125.91 (d, *J* = 8.1 Hz), 124.96 (d, *J* = 83.9 Hz), 124.06, 123.52 (d, *J* = 9.0 Hz), 122.95, 120.73 (q, *J* = 321.2 Hz), 117.38, 116.4 (d, *J* = 23.3 Hz), 115.36 (d, *J* = 88.8 Hz), 115.12 (d, *J* = 88.8 Hz), 114.44 (d, *J* = 22.2 Hz), 79.76, 72.91, 61.24, 40.78, 40.70, 31.32, 30.27, 24.50, 14.63 ; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -110.66 (t, *J* = 9.4 Hz), -78.16; ^{31}P (162 MHz, $CDCl_3$) δ: 20.63; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 821.2852, $C_{49}H_{44}ClFN_4O_3P^+$ requires 821.2824.

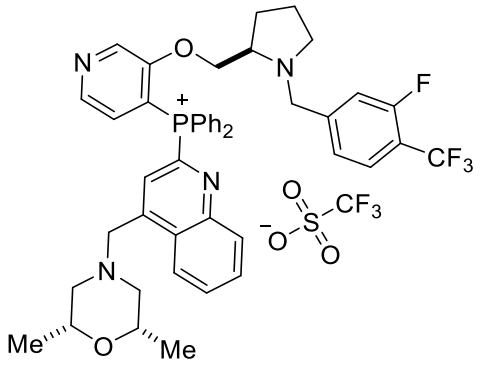
(4-(((2*R*, 6*S*)-2,6-Dimethylmorpholino)methyl)quinolin-2-yl)(3-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (3n)



Prepared according to general procedure B using 2-(3-fluoro-5-(pyridin-3-yl)phenyl)-6-methylpyridine (132 mg, 0.50 mmol), Tf_2O (84 μL, 0.50 mmol), (2*R*, 6*S*)-4-((2-(diphenylphosphaneyl)quinolin-4-yl)methyl)-2,6-dimethylmorpholine (242 mg, 0.55 mmol), DBU (75 μL, 0.50 mmol) and CH_2Cl_2 (5 mL). After the purification procedure, the title compound was isolated as an off white solid (317 mg, 0.37 mmol, 74% yield). mp 106-111 ºC; IR ν_{max}/cm^{-1} (film): 3063, 2971, 2930, 2856, 1575, 1439, 1263, 1223, 1143, 1030, 728; ^{1}H NMR (400 MHz,

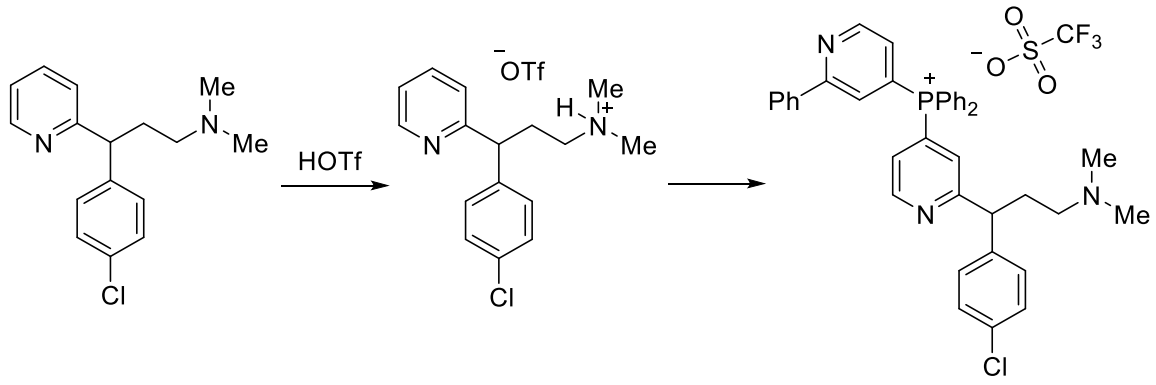
$CDCl_3$) δ: 9.03 (1H, app t, *J* = 4.7 Hz), 8.75 (1H, d, *J* = 6.8 Hz), 8.12 (1H, d, *J* = 8.4 Hz), 8.02-7.89 (6H, m), 7.88-7.75 (6H, m), 7.59 (1H, t, *J* = 7.7 Hz), 7.55-7.36 (4H, m), 7.05 (1H, d, *J* = 7.7 Hz), 6.93 (1H, s), 6.64 (1H, d, *J* = 7.8 Hz), 6.31 (1H, d, *J* = 8.2 Hz), 3.75 (2H, s), 3.43-3.21 (2H, m), 2.52-2.38 (5H, m), 1.83 (2H, t, *J* = 10.2 Hz) , 1.07 (6H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.04 (d, *J* = 249.4 Hz), 158.29, 152.53 (d, *J* = 7.4 Hz), 152.27 (d, *J* = 2.5 Hz), 150.80 (d, *J* = 10.5 Hz), 148.33 (d, *J* = 23.0), 147.71 (br), 144.34 (d, *J* = 118.4 Hz), 141.49 (d, *J* = 8.0 Hz), 139.73 (d, *J* = 7.3 Hz), 137.38-137.20 (m), 137.12, 136.08 (d, *J* = 3.1 Hz), 135.06 (d, *J* = 9.8 Hz), 131.61, 130.76 (d, *J* = 12.9 Hz), 130.22 (2C, m), 128.95 (d, *J* = 9.7 Hz), 128.39 (d, *J* = 85.0 Hz), 127.11 (d, *J* = 3.4 Hz), 123.26, 123.04 (d, *J* = 2.5 Hz), 122.91, 122.44 (d, *J* = 28.4 Hz) 120.85 (q, *J* = 321.3 Hz), 116.58 (d, *J* = 86.4 Hz), 116.55, 116.00 (d, *J* = 23.4 Hz), 113.76 (d, *J* = 22.6 Hz), 71.62, 59.29, 57.36, 24.58, 18.86; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.07, –111.47 (t, *J* = 10.2 Hz); ^{31}P (162 MHz, $CDCl_3$) δ: 11.94; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 703.2979, $C_{45}H_{41}FN_4OP^+$ requires 703.3002.

(4-(((*2S, 6R*)-2,6-Dimethylmorpholino)methyl)quinolin-2-yl)(3-(((*R*)-1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (3o)



Prepared according to general procedure B, using (*R*)-3-((1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridine (177 mg, 0.50 mmol), Tf_2O (85 μL, 0.50 mmol), (*2R, 6S*)-4-((2-(diphenylphosphaneyl)quinolin-4-yl)methyl)-2,6-dimethylmorpholine (242 mg, 0.55 mmol), DBU (75 μL, 0.89 mmol), and CH_2Cl_2 (5 mL). After the purification procedure (concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of 50% Et_2O in hexanes instead of Et_2O), the title compound was provided as a brown amorphous solid (310 mg, 0.33 mmol, 66% yield). IR ν_{max}/cm^{-1} (film): 3061, 3012, 2974, 2935, 2875, 2818, 1630, 1440, 909, 689, 665, 636, 603; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.75 (1H, d, *J* = 6.6 Hz), 8.65-8.60 (1H, m), 8.23 (1H, dd, *J* = 7.9, 0.7 Hz), 8.15 (1H, d, *J* = 8.4 Hz), 7.98-7.69 (13H, m), 7.34 (1H, t, *J* = 7.7 Hz), 7.12 (1H, dd, *J* = 19.6, 9.8 Hz), 6.85-6.69 (2H, m), 4.10-3.91 (4H, m), 3.53-3.40 (2H, m), 3.34 (1H, d, *J* = 14.2 Hz), 2.80 (1H, d, *J* = 13.8 Hz), 2.65-2.51 (3H, m), 2.07-1.87 (3H, m), 1.87-1.74 (1H, m), 1.69-1.54 (1H, m), 1.47-1.25 (3H, m), 1.11 (6H, app t, *J* = 5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.46 (dq, *J* = 257.36 257.4, 2.3 Hz), 155.69, 148.76 (d, *J* = 23.1 Hz), 148.24, (d, *J* = 11.2 Hz), 144.40 (d, *J* = 10.2 Hz), 143.96 (d, *J* = 120.6 Hz), 136.87 (m), 135.79 (m), 134.55-134.19 (m), 131.76, 130.66 (d, *J* = 13.2 Hz), 130.63, 129.17, 128.57, 128.27 (d, *J* = 73.9 Hz), 127.00-126.76 (m, 2C), 124.03, 123.86, 123.63 (d, *J* = 3.6 Hz), 122.37, 122.50 (dq, *J* = 273.6 Hz), 120.76 (q, *J* = 318.4 Hz), 116.78 (dd, *J* = 89.6, 3.1 Hz), 116.11 (dd, *J* = 91.4, 1.4 Hz), 114.57 (d, *J* = 86.2 Hz), 73.54, 71.64, 62.21, 59.64, 59.39 (d, *J* = 4.7 Hz), 58.10, 54.07, 27.83, 22.56, 19.96 (d, *J* = 3.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –61.13 (d, *J* = 13.74 13.7 Hz), –78.14, –114.39- (–)115.04 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 12.52; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 793.3407, $C_{46}H_{46}F_4N_4O_2P^+$ requires 793.3295.

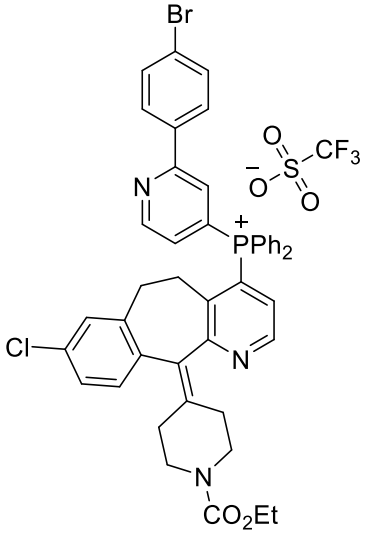
(2-(1-(4-Chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)diphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (3p)



Chlorphenamine (412.2 mg, 1.50 mmol) was dissolved in Et_2O (3 mL) and cooled to 0 °C. Trifluoromethanesulfonic acid (134 μL, 1.50 mmol) was added dropwise, the ice bath was removed and the solution was stirred for 10 minutes at room temperature. The solution was concentrated *in vacuo* and the resulting acid salt was subjected to general procedure B (except that after 4-(diphenylphosphino)-2-phenylpyridine was added, the reaction mixture was stirred for 30 min at −78 °C) using Tf_2O (252 μL, 1.50 mmol), 4-(diphenylphosphino)-2-phenylpyridine (560 mg, 1.65 mmol), DBU (450 μL, 3.00 mmol) and CH_2Cl_2 (15 mL). After the purification procedure, the title compound was isolated as a white amorphous powder (714 mg, 0.95 mmol, 63% yield). mp 130-133 °C; IR υ_{max}/cm^{-1} (film): 3060, 1574, 1489, 1468, 1440, 1378, 1259, 1223, 1150, 1124, 1109, 1028, 729, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.05 (1H, d, *J* = 5.2 Hz), 9.00 (1H, t, *J* = 5.2 Hz), 7.95-7.87 (4H, m), 7.80-7.77 (5H, m), 7.70-7.65 (4H, m), 7.52-7.45 (5H, m), 7.39 (1H, dd, *J* = 13.0, 4.8 Hz), 7.27 (2H, d, *J* = 8.3 Hz), 7.17 (2H, d, *J* = 8.3 Hz), 4.46 (1H, t, *J* = 7.4 Hz), 3.07-2.93 (2H, m), 2.83-2.76 (1H, m), 2.69 (6H, s), 2.44-2.35 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.22 (d, *J* = 9.6 Hz), 159.31 (d, *J* = 10.3 Hz), 151.77 (d, *J* = 10.9 Hz), 151.36 (d, *J* = 10.5 Hz), 139.50, 136.68 (d, *J* = 1.6 Hz), 136.48 (d, *J* = 2.5 Hz), 134.56 (d, *J* = 10.6 Hz), 133.05, 131.13,

130.99, 130.53, 129.42, 129.06, 128.98, 127.58 (d, J = 83.9 Hz), 127.27 (d, J = 83.6 Hz), 127.13, 125.31 (d, J = 8.3 Hz), 125.09 (d, J = 8.2 Hz), 123.20 (d, J = 8.8 Hz), 120.40 (q, J = 318.7 Hz), 114.01 (d, J = 88.9 Hz), 56.27, 49.15, 43.36, 29.65; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.30; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.06; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 612.2328, $C_{39}H_{36}ClN_3P^+$ requires 612.2335.

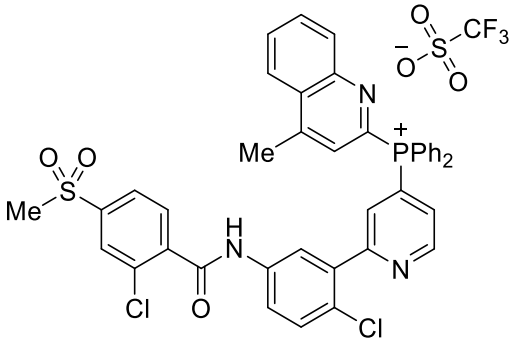
(2-(4-Bromophenyl)pyridin-4-yl)(8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (3q)



Prepared according to general procedure B using loratadine (383 mg, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 2-(4-Bromophenyl)-4-(diphenylphosphaneyl)pyridine (460 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After the purification procedure, the title compound was isolated as an off white solid (770 mg, 0.81 mmol, 81% yield). mp 159-164 ºC; IR ν_{max}/cm^{-1} (film): 3055, 2981, 1687, 1438, 1262, 1223, 1109, 1030, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.01 (1H, app t, J = 5.1 Hz), 8.73 (1H, app t, J = 4.7 Hz), 8.05-7.62 (13H, m), 7.60-7.40 (3H, m) 7.16 (1H, dd, J = 7.7, 5.1 Hz), 7.06 (2H, s), 6.63 (1H, s), 4.06 (2H, q, J = 6.8 Hz), 3.80-

3.57 (2H, m), 3.40-3.16 (3H, m) 2.74 (1H, d, *J* = 17.4 Hz), 2.63-2.09 (5H, m), 1.60-1.39 (1H, m), 1.20 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.34 (d, *J* = 8.5 Hz), 158.14 (d, *J* = 10.5 Hz), 155.15, 151.83 (d, *J* = 10.9 Hz), 149.26 (d, *J* = 11.6 Hz), 139.30, 136.53, 136.46-136.12 (2C, m), 135.45 (d, *J* = 1.4 Hz), 134.26 (d, *J* = 10.6 Hz), 133.83, 133.37, 132.17-131.89 (2C, m), 131.41, 131.20 (d, *J* = 13.2 Hz), 129.64, 128.71, 128.64 (d, *J* = 83.6 Hz), 127.54 (d, *J* = 10.3 Hz), 126.28, 125.35 (d, *J* = 8.3 Hz), 125.14 (d, *J* = 82.3 Hz), 122.94 (d, *J* = 8.9 Hz), 120.48 (q, *J* = 321.4 Hz), 114.84 (d, *J* = 88.2 Hz), 114.39 (d, *J* = 88.1 Hz), 61.17, 44.48, 44.34, 30.52, 30.43-30.10 (2C, m), 29.30, 14.45; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; ^{31}P (162 MHz, $CDCl_3$) δ: 20.87; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 798.1693, $C_{45}H_{39}BrClN_3O_2P^+$ requires 798.1652.

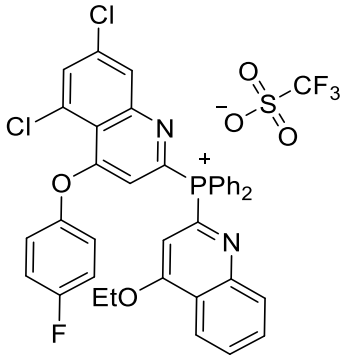
(2-(2-Chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (3r)



Prepared according to general procedure B (except the stirring time after the addition of Tf_2O was 2 hours instead of 30 minutes, the stirring time after the addition of the phosphine was 1.5 hours instead of 30 minutes, and after the addition of DBU the reaction was allowed to slowly warm from –78 ºC to 0 ºC over 3 hours instead of warming from –78 ºC to room temperature over approximately 15-30 minutes) using vismodegib (506 mg, 1.20 mmol), Tf_2O (200 μL, 1.20 mmol),

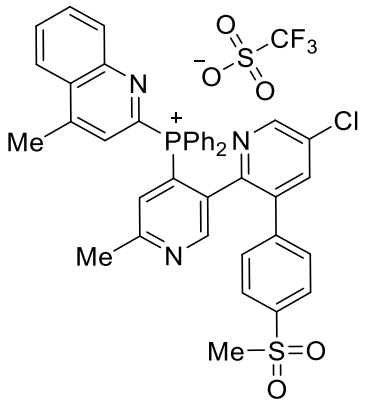
2-(diphenylphosphaneyl)-4-methylquinoline (432 mg, 1.32 mmol), DBU (180 μL, 1.20 mmol) and CH_2Cl_2 (30 mL). After the purification procedure (concentrated CH_2Cl_2 solution was added dropwise to an excess of Et_2O at room temperature. The resulting suspension was immediately filtered on a frit and the solid was washed with room temperature Et_2O. The solid was dissolved in approximately 5 mL CH_2Cl_2 and this process was repeated (4x) before the solid was dried *in vacuo* to provide the pure phosphonium salt), the title compound was isolated as a pale yellow solid (592 mg, 0.66 mmol, 55% yield). mp 119-125 ºC; IR ν_{max}/cm^{-1} (film): 3255, 3062, 1681, 1575, 1539, 1439, 1364, 1315, 1274, 1246, 1152, 1029, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.90 (1H, s), 8.98 (1H, app t, *J* = 5.1 Hz), 8.24-8.09 (3H, m), 8.01-7.59 (18H, m), 7.56 (1H, d, *J* = 4.8 Hz), 7.31-7.23 (1H, m), 2.93 (3H, s), 2.77 (3H, s) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.27, 157.96 (d, *J* = 10.9 Hz), 150.87 (d, *J* = 10.6 Hz), 148.76 (d, *J* = 10.9 Hz), 148.46 (d, *J* = 23.0 Hz), 142.65 (d, *J* = 118.3), 142.04, 140.23, 137.66, 136.79 (d, *J* = 1.6 Hz), 136.05 (d, *J* = 2.7 Hz), 134.58 (d, *J* = 10.3 Hz), 132.23, 131.83, 130.92-130.42 (2C, m), 130.29, 129.85, 128.77 (d, *J* = 3.1 Hz), 128.46 (d, *J* = 83.7 Hz), 128.59-128.24 (3C, m), 126.35, 125.82 (d, *J* = 7.6 Hz), 125.59, 125.10 (d, *J* = 27.0 Hz), 124.31, 123.07, 122.38, 120.24 (d, *J* = 320.9 Hz), 115.31 (d, *J* = 87.8 Hz), 44.14, 19.05 (d, *J* = 1.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.30; ^{31}P (162 MHz, $CDCl_3$) δ: 13.30; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 746.1185, $C_{41}H_{31}Cl_2N_3O_3PS^+$ requires 746.1201.

(5,7-Dichloro-4-(4-fluorophenoxy)quinolin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (3s)



Prepared according to general procedure B, using 5,7-dichloro-4-(4-fluorophenoxy)quinoline (308 mg, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 2-(diphenylphosphaneyl)-4-ethoxyquinoline (392 mg, 1.10 mmol), DBU (150 μL, 1.00 mmol), and EtOAc (10 mL). After the purification procedure (concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of 50% Et_2O in hexanes instead of Et_2O), the title compound was provided as a brown amorphous solid (400 mg, 0.49 mmol, 49% yield). IR ν_{max}/cm^{-1} (film): 3070, 2989, 2248, 855, 834, 646, 594, 572; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.31 (1H, d, J = 8.1 Hz), 8.02 (1H, d, J = 2.1 Hz), 7.87-7.64 (14H, m), 7.16-7.04 (3H, m), 7.00 (1H, d, J = 6.4 Hz), 6.96-6.88 (2H, m), 4.14 (2H, q, J = 7.0 Hz), 1.47 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.34 (d, J = 12.9 Hz), 153.30 (d, J = 14.0 Hz), 160.27 (d, J = 246.1 Hz), 151.68 (d, J = 25.5 Hz), 149.24 (d, J = 25.4 Hz), 148.30 (d, J = 117.4 Hz), 148.14 (d, J = 2.8 Hz), 144.56 (d, J = 116.9 Hz), 136.97, 135.54 (d, J = 2.9 Hz), 134.68 (d, J = 10.0 Hz), 132.24, 131.67, 131.09 (d, J = 1.2 Hz), 130.27 (d, J = 13.0 Hz), 129.13, 127.99, 122.77 (d, J = 8.6 Hz), 122.45, 121.56 (d, J = 2.3 Hz), 120.64 (q, J = 321.3 Hz), 118.17 (d, J = 2.3 Hz), 117.21, 116.96, 116.51 (d, J = 87.5 Hz), 110.93 (d, J = 26.9 Hz), 105.92 (d, J = 29.0 Hz), 65.51, 13.93; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −78.19, −114.90- (−)115.01 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 8.41; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 663.1166, $C_{38}H_{27}Cl_2FN_2O_2P^+$ requires 663.1199.

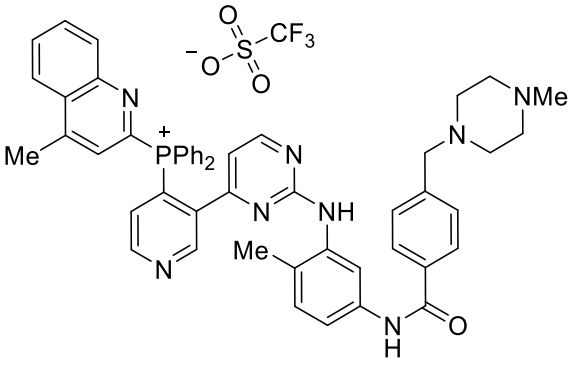
(5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (3t)



Prepared according to general procedure B except with NaOAc added with phosphine, using 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (538 mg, 1.50 mmol), Tf_2O (255 μL, 1.50 mmol), 2-(diphenylphosphaneyl)-4-methylquinoline (540 mg, 1.65 mmol), DBU (225 μL, 1.50 mmol), NaOAc (123 mg, 1.50 mmol) and CH_2Cl_2 (15 mL). After the purification procedure (concentrated CH_2Cl_2 solution was added dropwise to an excess of Et_2O at room temperature. The resulting suspension was immediately filtered on a frit and the solid was washed with room temperature Et_2O. The solid was dissolved in approximately 5 mL CH_2Cl_2 and this process was repeated (3x) before the solid was dried *in vacuo* to provide the pure phosphonium salt), the title compound was provided as a yellow crystalline solid (840 mg, 1.04 mmol, 69% yield). mp 165-170 ºC; IR ν_{max}/cm^{-1} (film): 3060, 1576, 1312, 770, 721, 547; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.24 (1H, d, *J* = 7.0 Hz), 8.12-7.93 (8H, m), 7.87-7.67 (9H, m), 7.62-7.55 (3H, m), 7.30-7.23 (2H, m), 3.17 (3H, s), 2.74 (3H, s), 2.60 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.87 (d, *J* = 11.1 Hz), 152.08 (d, *J* = 7.2 Hz), 148.24 (d, *J* = 11.1 Hz), 147.98 (d, *J* = 2.1 Hz), 147.32 (d, *J* = 24.0 Hz), 147.15 (d, *J* = 125.9 Hz), 146.15, 141.55, 141.15, 138.54, 135.30, 135.29, 135.13 (d,

J = 3.0 Hz), 134.85 (d, *J* = 9.4 Hz), 133.39 (d, *J* = 3.2 Hz), 131.95, 131.71, 130.71 (d, *J* = 10.1 Hz), 130.23, 130.07 (d, *J* = 6.3 Hz), 129.74 (d, *J* = 1.3 Hz), 128.92 (d, *J* = 87.0 Hz), 128.36, 128.12 (d, *J* = 3.1 Hz), 124.45, 123.53 (d, *J* = 26.9 Hz), 120.83 (q, *J* = 321.2 Hz), 119.37 (d, *J* = 88.5 Hz), 44.14, 24.62, 18.84 (d, *J* = 1.6 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.31; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 684.1666 $C_{40}H_{32}ClN_3O_2PS^+$ requires 684.1641.

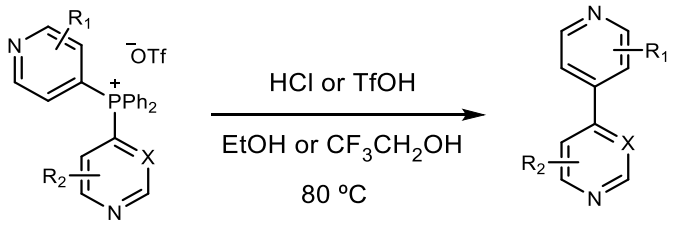
(3-(2-((2-Methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (3u)



Prepared according to general procedure B (except that the stirring time after addition of Tf_2O was 2 hours instead of 30 minutes, the stirring time after addition of 2-(diphenylphosphino)-4-methylquinoline was 1.5 hours instead of 30 minutes, and after the addition of DBU the reaction was allowed to slowly warm from –78 ºC to 0 ºC over 3 hours instead of warming from –78 ºC to room temperature over approximately 15-30 minutes) using (1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(benzyloxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (592 mg, 1.20 mmol), Tf_2O (200 μL, 1.20 mmol), 2-(diphenylphosphino)-4-methylquinoline (432 mg, 1.32 mmol), DBU (180 μL, 1.20 mmol) and CH_2Cl_2 (30 mL). After the purification procedure (concentrated CH_2Cl_2 solution was

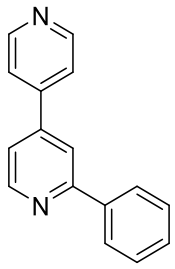
added dropwise to an excess of Et_2O at room temperature. The resulting suspension was immediately filtered on a frit and the solid was washed with room temperature Et_2O. The solid was dissolved in approximately 5 mL CH_2Cl_2 and this process was repeated (3x) before the solid was dried *in vacuo* to provide the pure phosphonium salt), the title compound was isolated as a yellow amorphous powder (710 mg, 0.73 mmol, 61% yield). mp 155-158 °C; IR υ_{max}/cm^{-1} (film): 3316, 3056, 2795, 1662, 1568, 1527, 1505, 1474, 1450, 1406, 1254, 1222, 1149, 1104, 1028, 857, 815, 752, 726, 689; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.52 (1H, d, *J* = 6.4 Hz), 9.04 (1H, dd, *J* = 4.8, 4.4 Hz), 8.53 (1H, s), 8.23 (1H, d, *J* = 5.1 Hz), 8.01–7.99 (1H, m), 7.87-7.59 (15H, m), 7.52 (1H, d, *J* = 4.8 Hz), 7.45 (1H, dd, *J* = 4.3, 2.0 Hz), 7.39 (2H, d, *J* = 8.2 Hz), 7.28 (1H, dd, *J* = 15.7, 5.1 Hz), 7.22 (1H, d, *J* = 5.2 Hz), 7.06 (1H, d, *J* = 1.9 Hz), 6.92 (1H, d, *J* = 8.5 Hz), 5.51 (1H, s), 3.54 (2H, s), 2.77-2.51 (14H, m), 1.50 (3H, s); ^{13}C NMR (100 MHz, CD_3CN) δ: 166.21, 161.17, 159.55 (d, *J* = 1.1 Hz), 159.01, 154.33 (d, *J* = 1.1 Hz), 152.10 (d, *J* = 6.3 Hz), 149.77 (d, *J* = 11.3 Hz), 149.43, 148.63, 148.38, 148.10, 142.66, 137.94, 136.82, 136.06 (d, *J* = 2.1 Hz), 135.71 (d, *J* = 9.3 Hz), 135.33 (d, *J* = 85.6 Hz), 132.86 (d, *J* = 9.8 Hz), 132.23, 131.02 (d, *J* = 12.7 Hz), 130.44 (d, *J* = 4.4 Hz), 129.85, 129.45 (d, *J* = 3.0 Hz), 128.45, 126.72, 126.06 (d, *J* = 84.5 Hz), 125.56 (d, *J* = 1.0 Hz), 123.30, 123.04, 122.31 (d, *J* = 90.6 Hz), 122.01 (q, *J* = 319.1 Hz), 117.99, 115.59, 110.10, 62.06, 55.02, 51.51, 44.62, 18.95 (d, *J* = 1.6 Hz), 17.29; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.13; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.51; *m/z* HRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 819.3695, $C_{51}H_{48}N_8OP^+$ requires 819.3689.

A 2.3.4 General Procedure C (Ligand-coupling Reactions to Make Heterobiaryls)



An oven dried 8 mL vial with a septa cap was charged with the phosphonium salt (1.0 equiv) and EtOH or TFE (0.4 M). The vial was subjected to three rapid cycles of vacuum / nitrogen backfill and then HCl or TfOH (2.0 equiv) was added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 80 ºC for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl.

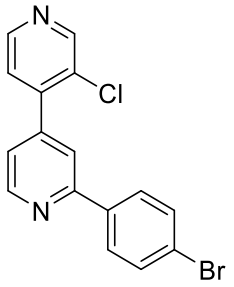
2-Phenyl-4,4'-bipyridine (4a)



Prepared according to general procedure C using diphenyl(2-phenylpyridin-4-yl)(pyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), 4.0 M HCl in dioxanes (250 µL, 1.00 mmol), and EtOH (1.25 mL). The was reaction was heated to 80 ºC for 14 hours. Flash column chromatography (silica gel, gradient elution: 40% EtOAc in hexanes to 50% EtOAc in hexanes)

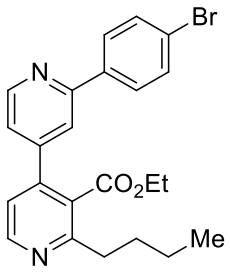
afforded the title compound as an off white solid (102 mg, 0.44 mmol, 88% yield). mp 64-65 ºC; IR ν_{max}/cm^{-1} (film): 3029, 1590, 1532, 1472, 1444, 1389, 1225, 808, 770, 731, 687; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.87-8.59 (3H, m), 8.02 (2H, d, *J* = 7.2 Hz), 7.88 (1H, s), 7.62-7.32 (6H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.34, 150.51, 150.34, 146.25, 145.67, 138.78, 129.21, 128.71, 126.86, 121.34, 119.70, 118.16; *m/z* HRMS (DART) found $[M+H]^+$ 233.1092, $C_{16}H_{13}N_2^+$ requires 233.1073.

2-(4-Bromophenyl)-3'-chloro-4,4'-bipyridine (4b)



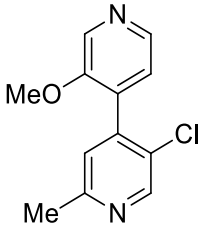
Prepared according to general procedure C using (2-(4-bromophenyl)pyridin-4-yl)(3-chloropyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (340 mg, 0.50 mmol), 4.0 M HCl in dioxanes (250 μL, 1.00 mmol), and EtOH (1.25 mL). The was reaction was heated to 80 ºC for 17 hrs. Flash column chromatography (silica gel: 25% EtOAc in hexanes) afforded the title compound as a white solid (111 mg, 0.32 mmol, 64% yield). mp 153-154 ºC; IR ν_{max}/cm^{-1} (film): 3053, 1603, 1579, 1552, 1461, 1412, 1376, 1111, 1006, 831, 741; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.79 (1H, d, *J* = 5.0 Hz), 8.74 (1H, s), 8.60 (1H, d, *J* = 4.9 Hz), 7.91 (2H, d, *J* = 8.5 Hz), 7.77 (1H, s), 7.61 (2H, d, *J* = 8.5 Hz), 7.37-7.28 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.61, 150.35, 149.96, 148.15, 145.03, 144.91, 137.56, 131.92, 129.72, 128.46, 124.53, 123.87, 122.03, 120.01; *m/z* HRMS (DART) found $[M+H]^+$ 344.9812, $C_{16}H_{11}BrN_2^+$ requires 344.9789.

Ethyl 2'-(4-bromophenyl)-2-butyl-[4,4'-bipyridine]-3-carboxylate (4c)



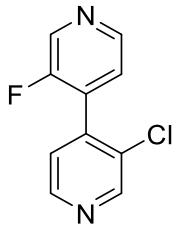
Prepared according to general procedure C using (2-(4-bromophenyl)pyridin-4-yl)(2-butyl-3-(ethoxycarbonyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (155 mg, 0.20 mmol), trifluoromethanesulfonic acid (36 μL, 0.40 mmol) and EtOH (0.5 mL) at 80 °C for 14 hours. Flash column chromatography (silica gel: 16% EtOAc in hexanes to 33% EtOAc in hexanes) afforded the title compound as a colorless oil (67 mg, 0.15 mmol, 76% yield). IR υ_{max}/cm^{-1} (film): 3051, 2956, 2929, 2870, 1722, 1601, 1589, 1575, 1537, 1491, 1475, 1455, 1405, 1379, 1258, 1138, 1099, 1071, 1045, 1008, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, d, J = 5.0 Hz), 8.68 (1H, d, J = 5.0 Hz), 7.90 (2H, d, J = 8.3 Hz), 7.71 (1H, s), 7.60 (2H, d, J = 8.3 Hz), 7.26 (1H, d, J = 5.8 Hz), 7.18 (1H, d, J = 5.0 Hz), 4.11 (2H, q, J = 7.2 Hz), 2.89 (2H, t, J = 7.8 Hz), 1.76 (2H, qn, J = 7.6 Hz), 1.42 (2H, sext, J = 7.4 Hz), 1.00 (3H, t, J = 7.2 Hz), 0.94 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.97, 160.08, 156.52, 150.14, 149.95, 147.22, 145.26, 137.49, 131.99, 128.40, 127.85, 123.92, 121.29, 120.68, 119.21, 61.69, 36.02, 31.93, 22.66, 13.86, 13.60; *m/z* HRMS (DART) found $[M+H]^+$ 439.1029, $C_{23}H_{23}BrN_2O_2^+$ requires 439.1021.

5-Chloro-3'-methoxy-2-methyl-4,4'-bipyridine (4d)



Prepared according to general procedure C using (5-chloro-2-methylpyridin-4-yl)(3-methoxypyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (285 mg, 0.50 mmol), trifluoromethanesulfonic acid (89 μL, 1.00 mmol) and EtOH (1.25 mL) at 80 °C for 14 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a colorless crystalline solid (77 mg, 0.33 mmol, 65% yield). mp 105-108 °C; IR υ_{max}/cm^{-1} (film): 3029, 2968, 2938, 2842, 1582, 1556, 1506, 1492, 1469, 1441, 1379, 1360, 1312, 1306, 1291, 1269, 1256, 1239, 1213, 1195, 1101, 1017, 846, 833; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (1H, s), 8.39 (1H, s), 8.33 (1H, d, *J* = 4.7 Hz), 7.09 (1H, d, *J* = 4.7 Hz), 7.05 (1H, s), 3.88 (3H, s), 2.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.62, 152.18, 148.70, 142.83, 142.52, 134.21, 133.11, 128.01, 124.66, 124.11, 56.18, 23.74; *m/z* HRMS (DART) found $[M+H]^+$ 235.0664, $C_{12}H_{12}ClN_2O^+$ requires 235.0638.

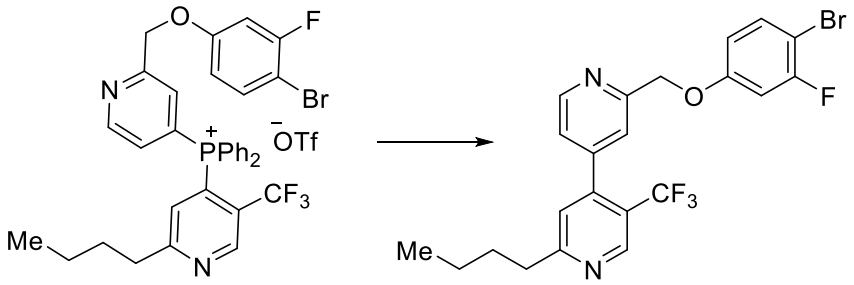
3-Chloro-3'-fluoro-4,4'-bipyridine (4e)



Prepared according to general procedure C using (3-chloro-pyridin-4-yl)(3-fluoropyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (136 mg, 0.25 mmol), 4.0M HCl in dioxane (125 μL, 0.50 mmol) and EtOH (0.625 mL) at 80 °C for 23 hours. Flash column chromatography (silica gel: 40% EtOAc in hexanes to 50% EtOAc in hexanes) followed by flash column chromatography (neutral alumina: 20% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a white crystalline solid (34 mg, 0.16 mmol, 65% yield). mp 92-94 °C; IR υ_{max}/cm^{-1} (film): 3021, 1578, 1470, 1413, 1398, 1268, 1217, 1202, 1176, 1110, 1027, 830, 752; ^{1}H

NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, s), 8.60-8.44 (3H, m), 7.29-7.17 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.86 (d, *J* = 259.5 Hz), 150.15, 147.84, 145.81 (d, *J* = 5.4 HZ), 139.81, 139.05 (d, *J* = 24.1 Hz), 131.57 (d, *J* = 13.0 Hz), 130.70, 124.97, 124.63; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −128.06 (d, *J* = 5.5 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 209.0, $C_{10}H_7ClFN_2^+$ requires 209.0.

2'-((4-Bromo-3-fluorophenoxy)methyl)-2-butyl-5-(trifluoromethyl)-4,4'-bipyridine (4f)

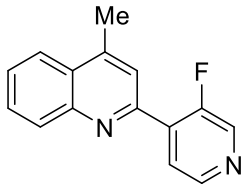


isolated as mixture see 3f

Prepared according to general procedure C using (2-((4-bromo-3-fluorophenoxy)methyl)pyridin-4-yl)(2-butyl-5-(trifluoromethyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (204 mg, isolated as a mixture see 3f), Trifluoromethanesulfonic acid (45 μL, 0.50 mmol) and EtOH (0.625 mL) at 80 °C for 12 hours. Flash column chromatography (silica gel: 2% EtOAc in CH_2Cl_2 to 5% EtOAc in CH_2Cl_2) afforded the title compound as a white amorphous powder (63 mg, 0.13 mmol, 29% yield over two steps). mp 79-81 °C; IR υ_{max}/cm^{-1} (film): 3027, 2958, 2924, 2875, 2860, 1597, 1589, 1564, 1539, 1492, 1467, 1452, 1426, 1415, 1380, 1323, 1292, 1268, 1249, 1189, 1177, 1153, 1130, 1101, 1089, 1057, 1032, 974, 942, 902, 855, 843, 820; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.88 (1H, s), 8.68 (1H, d, *J* = 5.0 Hz), 7.44-7.38 (2H, m), 7.22 (1H, d, *J* = 4.8 Hz), 7.08 (1H, s), 6.78 (1H, dd, *J* = 10.2, 2.8 Hz), 6.69 (1H, dd, *J* = 8.9, 2.8 Hz), 5.22 (2H, s), 2.88 (2H, t, *J* = 7.7 Hz), 1.74 (2H, qn, *J* = 7.3 Hz), 1.40 (2H, sext, *J* = 7.5 Hz), 0.94 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.90,

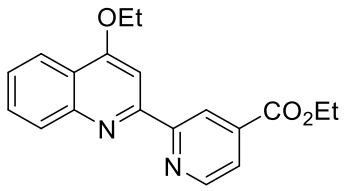
159.44 (d, J = 245.7 Hz), 158.68 (d, J = 9.7 Hz), 156.50, 149.21, 147.06 (q, J = 5.5 Hz), 146.29, 146.23 (q, J = 1.8 Hz), 133.47 (d, J = 1.7 Hz), 123.90, 123.50 (q, J = 272.3 Hz), 122.27 (d, J = 1.1 Hz), 121.38 (q, J = 30.6 Hz), 120.59, 111.98 (d, J = 3.2 Hz), 103.98 (d, J = 25.6 Hz), 100.11 (d, J = 21.2 Hz), 70.86, 37.99, 31.58, 22.44, 13.83; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –56.55, –104.87 (t, J = 8.4 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 483.0690, $C_{22}H_{20}BrF_4N_2O^+$ requires 483.0695.

2-(3-Fluoropyridin-4-yl)-4-methylquinoline (4g)



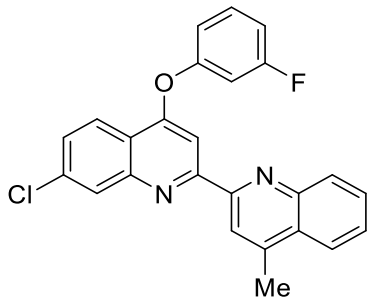
Prepared according to general procedure C, using (3-fluoropyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (286 mg, 0.50 mmol), 4.0M HCl in dioxane (250 μL, 1.00 mmol), and EtOH (1.25 mL) at 80 °C for 12 hours. The crude material was purified by flash chromatography (silica gel gradient elution: 25% EtOAc in hexanes to 50% EtOAc in hexanes) to provide the title compound as a white crystalline solid (68 mg, 0.31 mmol, 57% yield). mp 94-95 °C; IR ν_{max}/cm^{-1} (film): 3038, 2968, 1464, 1350, 1277, 1235, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (1H, d, J = 2.8 Hz), 8.59 (1H, dd, J = 4.9, 0.9 Hz), 8.19 (1H, dd, J = 8.4, 0.5 Hz), 8.10 (1H, dd, J = 7.3, 5.0 Hz), 8.05 (1H, dd, J = 8.4, 0.9 Hz), 7.80-7.75 (2H, m), 7.66-7.62 (1H, m), 2.80 (3H, d, J = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.28 (d, J = 258.8 Hz); 158.84 (d, J = 2.0 Hz), 148.09, 146.25 (d, J = 5.1 Hz), 145.16, 139.33 (d, J = 26.1 Hz), 134.60 (d, J = 9.5 Hz), 130.50, 129.74, 127.79, 127.20, 124.58, 123.74, 122.69 (d, J = 8.2 Hz), 19.00; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –131.61 (d, J = 7.5 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 239.0973, $C_{15}H_{12}FN_2^+$ requires 239.0979.

Ethyl 2-(4-ethoxyquinolin-2-yl)isonicotinate (4h)



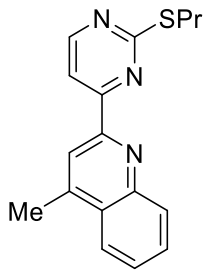
Prepared according to general procedure C, using (4-(ethoxycarbonyl)pyridin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (164 mg, 0.25 mmol), trifluoromethanesulfonic acid (42 μL, 0.50 mmol), and EtOH (0.63 mL) at 80 ºC for 12 hours. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes to 25% EtOAc in hexanes) to provide the title compound as a white crystalline solid (38 mg, 0.12 mmol, 47% yield). mp 102-104 ºC; IR ν_{max}/cm^{-1} (film): 3038, 2968, 1464, 1350, 1277, 1235, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.18 (1H, s), 8.84 (1H,d, *J* = 5.0 Hz), 8.26 (1H,dd, *J* = 3.16 3.2, 1.2 Hz), 8.15 (1H, d, *J* = 8.4 Hz), 7.97 (1H, s), 7.97 (1H, dd, *J* = 5.0, 1.6 Hz), 7.71-7.70 (1H, m), 7.56-7.49 (1H, m), 4.55-4.38 (4H, m), 1.62 (3H, t, *J* = 7.0 Hz), 1.47 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.36, 162.43, 157.71, 156.56, 149.59, 148.98, 138.80, 129.89, 129.35, 125.93, 123.05, 121.94, 121.54, 121.16, 98.12, 64.34, 61.83, 14.55, 14.29; *m/z* HRMS (DART) found $[M+H]^+$ 323.1386, $C_{19}H_{19}N_2O_3^+$ requires 323.1390.

7-Chloro-4-(3-fluorophenoxy)-4'-methyl-2,2'-biquinoline (4i)



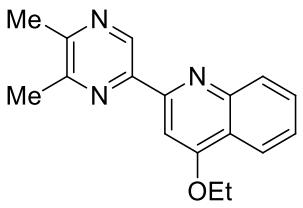
Prepared according to general procedure C, using (7-chloro-4-(3-fluorophenoxy)quinolin-2-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (187 mg, 0.25 mmol), trifluoromethanesulfonic acid (42 μL, 0.50 mmol), and (2,2,2)-Trifluoroethanol (0.63 mL) at 80ºC for 12 hours. The crude material was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to provide the title compound as a white crystalline solid (70 mg, 0.17 mmol, 67% yield). mp 208-210 ºC; IR ν_{max}/cm^{-1} (film): 3068, 1615, 1094, 947, 831, 755, 526; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (1H, d, *J* = 0.8 Hz), 8.28 (1H, d, *J* = 8.9 Hz), 8.25 (1H, d, *J* = 1.8 Hz), 8.13 (1H, s), 8.07 (1H, dd, *J* = 8.4, 0.7 Hz), 8.03 (1H, dd, *J* = 8.3, 0.9 Hz), 7.69 (1H, m), 7.60-7.53 (2H, m), 7.47 (1H, td, *J* = 12.2, 7.5 Hz), 7.10-6.99 (3H, m), 2.83 (3H, d, *J* = 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.60 (d, *J* = 248.4 Hz), 161.43, 158.99, 155.76 (d, *J* = 10.6 Hz), 154.93, 150.04, 147.57, 145.07, 136.33, 131.10, (d, *J* = 9.6 Hz), 130.50, 129.22, 128.57, 128.54, 127.50, 126.90, 123.75, 123.26, 120.13, 119.70, 116.32 (d, *J* = 3.4 Hz), 112.44 (d, *J* = 21.1 Hz), 108.65 (d, *J* = 24.2 Hz), 108.65 (d, *J* = 24.2 Hz), 103.43, 18.95; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −109.72-(−)109.79 (m); *m/z* HRMS (DART) found $[M+H]^+$ 415.1024, $C_{25}H_{17}ClFN_2O^+$ requires 415.1008.

4-Methyl-2-(2-(propylthio)pyrimidin-4-yl)quinoline (4j)



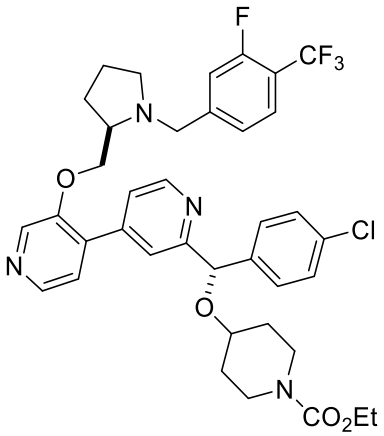
Prepared according to general procedure C using (4-Methylquinolin-2-yl)diphenyl(2-(propylthio)pyrimidin-4-yl)phosphonium trifluoromethanesulfonate (149 mg, 0.25 mmol), trifluoromethanesulfonic acid (44 μL, 0.50 mmol), and EtOH (0.63 mL). The was reaction was heated to 80 ºC for 5.5 hours. Flash column chromatography (silica gel: 5% EtOAc in hexanes) followed by a second flash column (silica gel, gradient elution: 3% EtOAc in hexanes to 5% EtOAc in hexanes) afforded the title compound as a white solid (27 mg, 0.091 mmol, 37% yield). mp 57-58 ºC; IR ν_{max}/cm^{-1} (film): 2925, 1557, 1539, 1505, 1417, 1352, 1317, 1194, 1160, 782; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (1H, d, *J* = 4.7 Hz), 8.40 (1H, s), 8.23 (1H, d, *J* = 4.7 Hz), 8.17 (1H, d, *J* = 8.1 Hz), 8.03 (1H, d, *J* = 8.1 Hz), 7.75 (1H, t, *J* = 7.0 Hz), 7.61 (1H, t, *J* = 7.0 Hz), 3.26 (2H, t, *J* = 7.1 Hz), 2.80 (3H, s), 1.88 (2H, sext, *J* = 7.1 Hz), 1.13 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.21, 163.22, 158.12, 153.22, 147.70, 145.37, 130.61, 129.53, 128.96, 127.37, 123.80, 119.29, 112.97, 33.04, 22.72, 19.02, 13.62; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 296.2, $C_{17}H_{18}N_3S^+$ requires 296.1.

2-(5,6-Dimethylpyrazin-2-yl)-4-ethoxyquinoline (4k)



Prepared according to general procedure C using (5,6-dimethylpyrazin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (154 mg, 0.25 mmol), trifluoromethanesulfonic acid (67 μL, 0.75 mmol) and EtOH (625 μL) at 100 °C for 14 hours. Flash column chromatography (silica gel: 33% EtOAc in hexanes) afforded the title compound as a gray amorphous powder (16 mg, 0.06 mmol, 23% yield). mp 189-191 °C; IR υ_{max}/cm^{-1} (film): 3080, 2999, 2977, 2919, 1615, 1586, 1500, 1472, 1460, 1445, 1420, 1402, 1376, 1359, 1347, 1273, 1249, 1232, 1185, 1156, 1114, 1105, 1089, 1027, 993, 953, 919, 861, 837, 818, 784, 777, 767; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52 (1H, s), 8.24 (1H, d, *J* = 8.2 Hz), 8.10 (1H, d, *J* = 8.4 Hz), 7.86 (1H, s), 7.71 (1H, dd, *J* = 7.2, 7.1 Hz), 7.50 (1H, dd, *J* = 7.8, 7.3 Hz), 4.42 (2H, q, *J* = 7.0 Hz), 2.64 (3H, s), 2.62 (3H, s), 1.61 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.28, 156.03, 152.39, 150.85, 149.00, 148.17, 140.21, 129.87, 129.28, 125.77, 121.89, 121.37, 97.86, 64.26, 22.23, 22.02, 14.55; *m/z* LRMS (DART) found $[M+H]^+$ 280.2, $C_{17}H_{18}N_3O^+$ requires 280.1.

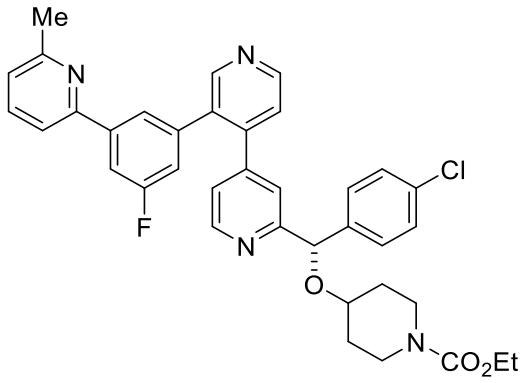
Ethyl 4-((*S*)-(4-chlorophenyl)(3'-(((*R*)-1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)-[4,4'-bipyridin]-2-yl)methoxy)piperidine-1-carboxylate (4l)



Prepared according to general procedure C, using (2-((*S*)-(4-chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)(3-(((*R*)-1-(3-fluoro-4-

(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (106 mg, 0.10 mmol), trifluoromethanesulfonic acid (25 μL, 0.30 mmol), and EtOH (0.25 mL) at 80 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 2% MeOH in CH_2Cl_2) followed by a second flash chromatography column (silica gel: 2% MeOH in CH_2Cl_2) to provide the title compound as a faint brown oil (43 mg, 0.06 mmol, 60% yield). IR ν_{max}/cm^{-1} (film): 3055, 2928, 2872, 1689, 1629, 1604, 1586, 1564, 1502, 964, 766, 645, 619, 534; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (1H, d, *J* = 5.5 Hz), 8.35-8.25 (2H, m), 7.62 (1H, s), 7.40-7.34 (1H, s), 7.40-7.34 (3H, m), 7.24 (1H, t, *J* = 1.7 Hz), 7.22 (2H, m), 6.93-6.85 (2H, m), 5.60 (1H, s), 4.05 (2H, q, *J* = 7.1 Hz), 3.95 (2H, d, *J* = 5.4 Hz), 3.79-3.62 (3H, m), 3.57 (1H, m), 3.17-3.04 (3H, m), 2.86-2.72 (2H, m), 2.10 (1H, q, *J* = 8.4 Hz), 1.96-1.47 (5H, m), 1.25-1.12 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.94, 159.72 (dq, *J* = 255.5, 2.3 Hz), 155.47, 151.76 (m), 148.82, 147.49 (d, *J* = 7.2 Hz), 144.64, 143.16, 140.14, 135.40, 134.77, 133.47, 128.65, 128.08, 126.75 (2C, m), 122.64 (dq, *J* = 270.5, 1.1 Hz), 123.86 (m), 123.22 (d, *J* = 3.4 Hz), 122.58, 116.09 (d, *J* = 20.7 Hz), 72.80, 62.61, 61.28, 58.75, 54.74, 41.07, 40.99, 31.16, 31.01, 29.67, 28.59, 23.26, 14.66; ^{19}F NMR δ: –61.13 (d, *J* = 12.8 Hz), –114.89-(–)115.21 (m); *m/z* HRMS (DART) found $[M+H]^+$ 727.2688, $C_{38}H_{40}ClF_4N_4O_4^+$ requires 727.2669.

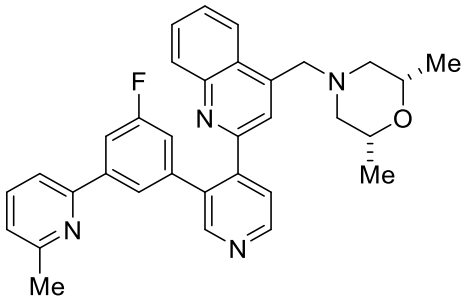
Ethyl (*S*)-4-((4-chlorophenyl)(3'-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)-[4,4'-bipyridin]-2-yl)methoxy)piperidine-1-carboxylate (4m)



Prepared according to general procedure C using (*S*)-(2-((4-chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)(3-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (97 mg, 0.10 mmol), trifluoromethanesulfonic acid (26.5 μL, 0.30 mmol), and EtOH (0.25 mL). The was reaction was heated to 80 ºC for 26 hours. Flash column chromatography (the crude reaction mixture was dissolved in 5 mL of CH_2Cl_2 and then 1 mL of trifluoroacetic acid was added, the mixture was loaded onto a silica column and then gradient elution: CH_2Cl_2 to 3% MeOH in CH_2Cl_2) followed by a second flash column (the crude reaction mixture was dissolved in 5 mL of CH_2Cl_2 and then 1 mL of trifluoroacetic acid was added, the mixture was loaded onto a silica column and then gradient elution: CH_2Cl_2 to 2% MeOH in CH_2Cl_2) followed by preparatory thin layer chromatography (silica gel: 3% MeOH in CH_2Cl_2 afforded the title compound as a colorless oil (41 mg, 0.07 mmol, 65% yield). IR ν_{max}/cm^{-1} (film): 3060, 2953, 2925, 1690, 1585, 1576, 1432, 1384, 1228, 1087, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (2H, br s), 8.54 (1H, d, *J* = 5.0 Hz), 7.69 (1H, d, *J* = 9.9 Hz), 7.60-7.50 (2H, m), 7.35 (1H, d, *J* = 4.2 Hz), 7.24-7.15 (3H, m), 7.13-7.04 (5H, m), 6.84 (1H, d, *J* = 8.7 Hz), 5.47 (1H, s), 4.09 (2H, q, *J* = 7.2 Hz), 3.63-3.49 (2H, m), 3.49-3.38 (1H, m), 3.16-3.03 (2H, m), 2.58 (3H, s), 1.72-1.55 (2H, m), 1.54-1.36 (2H, m), 1.23 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.95 (d, *J* = 246.7 Hz), 161.95, 158.64, 155.38,

154.23 (d, *J* = 2.9 Hz), 151.02, 149.66-149.29 (2C, m), 147.16, 145.05, 142.20 (d, *J* = 7.8 Hz), 139.54, 138.93 (d, *J* = 8.3 Hz), 136.94, 134.56, 133.30, 128.52, 127.81, 124.11-123.81 (2C, m), 122.47, 122.44, 120.99, 117.20, 116.54 (d, *J* = 22.6 Hz), 113.28 (d, *J* = 22.7 Hz), 80.38, 72.19, 61.19, 40.78, 40.72, 30.88, 30.68, 24.62, 14.66; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -112.23; *m/z* HRMS (ESI) found $[M+H]^+$ 637.2391, $C_{37}H_{35}ClFN_4O_3^+$ requires 637.2376.

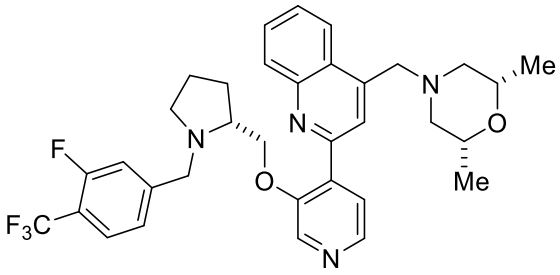
(2*R*, 6*S*)-4-((2-(3-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)pyridin-4-yl)quinolin-4-yl)methyl)-2,6-dimethylmorpholine (4n)



Prepared according to general procedure C (except an additional 18 μL, 0.20 mmol of trifluoromethanesulfonic acid was added after 40.5 hours) using (4-(((2*R*, 6*S*)-2,6-dimethylmorpholino)methyl)quinolin-2-yl)(3-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (85 mg, 0.10 mmol), trifluoromethanesulfonic acid (35 μL, 0.40 mmol), and EtOH (0.25 mL). The was reaction was heated to 80 ºC for 58.5 hours. Flash column chromatography (silica gel: 60% EtOAc in hexanes) followed by a second flash column (silica gel, gradient elution: 1% MeOH in CH_2Cl_2 to 2.5% MeOH in CH_2Cl_2) afforded the title compound as a colorless oil (23.7 mg, 0.046 mmol, 46%). IR ν_{max}/cm^{-1} (film): 3063, 2972, 2928, 1586, 1455, 1430, 1344, 1083, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (2H, br s), 8.27-8.15 (2H, m), 7.85-7.73 (3H, m), 7.68 (1H, d, *J* = 9.9 Hz), 7.58 (1H, t, *J* = 7.6 Hz), 7.51 (1H, t, *J* = 7.7 Hz), 7.23 (1H, d, *J* = 7.7 Hz), 7.15-7.03 (2H, m), 6.92 (1H,

d, *J* = 9.0 Hz), 3.63 (2H, s), 3.54-3.38 (2H, m), 2.50 (3H, s), 2.40 (2H, d, *J* = 11.5 Hz), 1.63 (2H, t, *J* = 10.5 Hz), 1.00 (6H, d, *J* = 6.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.86 (d, *J* = 246.4), 158.62, 156.36, 154.36 (d, *J* = 2.7 Hz), 150.76, 149.56, 148.57, 146.77, 143.77, 142.18 (d, *J* = 8.6 Hz), 139.74 (d, *J* = 8.2 Hz), 136.94, 134.58, 130.19, 129.63, 126.87, 126.64, 124.68, 124.24, 123.95 (d, *J* = 2.7 Hz), 122.63, 122.40, 117.22, 116.79 (d, *J* = 22.5 Hz), 113.16 (d, *J* = 22.7 Hz), 71.51, 59.81, 59.38, 24.51, 18.83; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -112.28 (t, *J* = 9.3 Hz); *m/z* HRMS (ESI) found $[M+H]^+$ 519.2572, $C_{33}H_{32}FN_4O^+$ requires 519.2555.

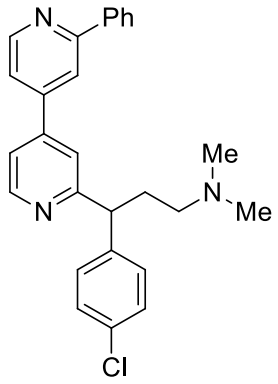
(*2S, 6R*)-4-((2-(3-(((*R*)-1-(3-Fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)quinolin-4-yl)methyl)-2,6-dimethylmorpholine (4o)



Prepared according to general procedure C, using (4-(((*2S, 6R*)-2,6-dimethylmorpholino)methyl)quinolin-2-yl)(3-(((*R*)-1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (94 mg, 0.10 mmol), 4.0M HCl in dioxane (100 μL, 0.40 mmol), and EtOH (0.25 mL) at 80 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 2% MeOH in CH_2Cl_2) to provide the title compound as a brown amorphous solid (30 mg, 0.05 mmol, 49% yield). IR ν_{max}/cm^{-1} (film): 3063, 2971, 2930, 2871, 2813, 1629, 1587, 1545, 693, 653, 602, 550, 531, 526; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50-8.39 (2H, m), 8.23 (1H, d, *J* = 8.3 Hz), 8.11 (1H, d, *J* = 8.4 Hz), 7.85 (1H, s), 7.75 (1H, d, *J* = 4.8 Hz), 7.71 (1H, m), 7.56 (1H,

m), 7.29 (1H, t, *J* = 7.7 Hz), 6.97-6.87 (2H, m), 4.21-4.06 (2H, m), 4.01 (1H, d, *J* = 14.16 14.2 Hz), 3.80 (2H, d, *J* = 1.8 Hz), 3.73-3.61 (2H, m), 3.30 (1H, d, *J* = 14.2 Hz), 3.08-2.97 (1H, m), 2.91-2.80 (1H, m), 2.79 (2H, d, *J* = 11.5 Hz), 2.15 (1H, q, *J* = 6.2 Hz), 2.06-1.94 (1H, m), 1.86 (2H, q, *J* = 10.6 Hz), 1.78-1.65 (3H, m), 1.14 (6H, d, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.57 (dq, *J* = 253.8, 2.1 Hz), 154.01, 152.42, 148.39, 147.22 (d, *J* = 5.5 Hz), 143.38, 143.23, 136.59, 135.72, 130.16, 129.47, 126.94-126.32 (m, 4C), 124.75, 124.17, 123.30 (d, *J* = 3.3 Hz), 122.97, 122.62 (dq, *J* = 273.1, 1.0 Hz), 116.89 (d, *J* = 20.6 Hz), 73.11, 71.67 (d, *J* = 2.2 Hz), 62.43, 60.13, 59.69 (d, *J* = 8.4 Hz), 58.86, 54.66, 28.60, 23.29, 19.88 (d, *J* = 1.1 Hz); ^{19}F NMR δ: –61.10 (d, *J* = 12.9 Hz), –114.67- (–)115.23 (m); *m/z* HRMS (DART) found $[M+H]^+$ 609.2839, $C_{34}H_{37}F_4N_4O_2^+$ requires 609.2847.

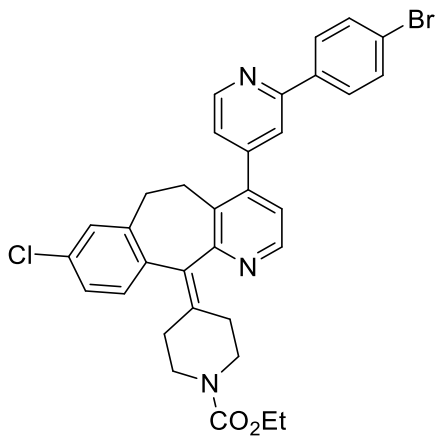
3-(4-Chlorophenyl)-N,N-dimethyl-3-(2'-phenyl-[4,4'-bipyridin]-2-yl)propan-1-amine (4p)



Prepared according to general procedure C using (2-(1-(4-chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)diphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (381 mg, 0.50 mmol), trifluoromethanesulfonic acid (134 μL, 1.50 mmol) and EtOH (1.25 mL) at 80 °C for 12 hours. Flash column chromatography (silica gel: 9% MeOH in CH_2Cl_2) afforded the title compound as a light yellow oil (179 mg, 0.42 mmol, 84% yield). IR υ_{max}/cm^{-1} (film): 3410, 3027, 2940, 2856, 2815, 2766, 2430, 2203, 1590, 1533, 1488,

1467, 1445, 1379, 1261, 1089, 1025, 1014, 907, 829, 775, 756, 727, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (1H, d, *J* = 4.9 Hz), 8.68 (1H, d, *J* = 4.9 Hz), 8.01 (2H, d, *J* = 7.4 Hz), 7.87 (1H, s), 7.49–7.33 (8H, m), 7.25 (2H, d, *J* = 8.6 Hz), 4.29 (1H, t, *J* = 7.4 Hz), 2.70–2.34 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.01, 158.27, 150.26, 150.06, 146.48, 146.27, 141.11, 138.76, 132.47, 129.21, 129.15, 128.66, 126.88, 120.96, 119.79, 119.49, 118.23, 56.90, 49.98, 44.25, 31.30; *m/z* HRMS (DART) found $[M+H]^+$ 428.1921, $C_{27}H_{27}ClN_3^+$ requires 428.1894.

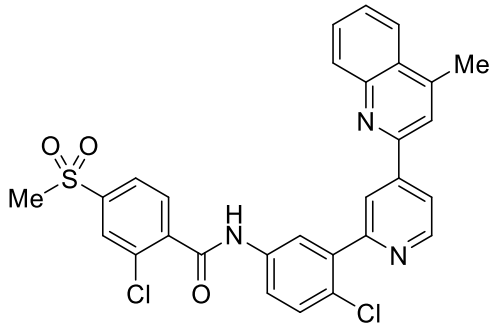
Ethyl 4-(4-(2-(4-bromophenyl)pyridin-4-yl)-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (4q)



Prepared according to general procedure C using (2-(4-bromophenyl)pyridin-4-yl)(8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (237 mg, 0.25 mmol), trifluoromethanesulfonic acid (44 μL, 0.50 mmol), and EtOH (625 μL). The was reaction was heated to 80 ºC for 30 hrs. Flash column chromatography (basic alumina, gradient elution: 20% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a white solid (133 mg, 0.22 mmol, 87% yield). mp 95-98 ºC; IR ν_{max}/cm^{-1} (film): 3050, 2972, 2922, 1690, 1578, 1473, 1428, 1222, 1008, 826, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (1H, d, *J* = 5.0 Hz), 8.49

(1H, d, *J* = 5.0 Hz), 7.91 (2H, d, *J* = 8.6 Hz), 7.66-7.58 (3H, m), 7.21-7.14 (3H, m), 7.12 (1H, s) 7.06 (1H, d, *J* = 5.0 Hz), 4.14 (2H, q, *J* = 7.2 Hz), 3.82 (2H, br s), 3.41-3.29 (1H, m), 3.27-3.12 (3H, m), 2.88-2.72 (2H, m), 2.56-2.35 (3H, m), 2.34-2.20 (1H, m), 1.26 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.73, 156.58, 155.34, 149.87, 147.81, 147.09, 146.77, 138.50, 137.53, 137.34, 135.89, 134.11, 133.01, 131.90, 131.21, 130.30, 129.60, 128.41, 126.07, 123.84, 122.53, 121.87, 119.70, 61.24, 44.69, 44.57, 32.12, 30.60, 30.51, 27.48, 14.48; *m/z* HRMS (DART) found $[M+H]^+$ 614.1235, $C_{33}H_{30}BrClN_3O_2^+$ requires 614.1204.

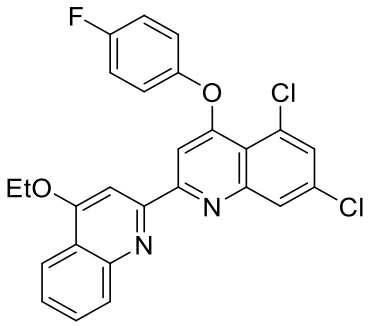
2-Chloro-N-(4-chloro-3-(4-(4-methylquinolin-2-yl)pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (4r)



Prepared according to general procedure C using (2-(2-chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (224 mg, 0.25 mmol), 4.0 M HCl in dioxanes (125 μL, 0.50 mmol), and (2,2,2)-Trifluoroethanol (625 μL). The was reaction was heated to 80 ºC for 37 hours. Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then gradient elution: CH_2Cl_2 to 1.5% MeOH in CH_2Cl_2) followed by a second flash column (basic alumina, gradient elution: CH_2Cl_2 to 2% MeOH in CH_2Cl_2) and the resulting solid was washed on a frit with 200 mL of Et_2O and then 25 mL of chilled CH_2Cl_2 (0 ºC). The title compound was isolated as a white solid (73 mg, 0.13 mmol, 52% yield). decomp. 270-275 ºC; IR ν_{max}/cm^{-1} (film): 3318, 3018,

2992, 2914, 1689, 1539, 1299, 1152, 1030, 816, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.99, (1H, s), 8.89 (1H, d, *J* = 5.2 Hz), 8.28 (1H, d, *J* = 5.2 Hz), 8.21 (1H, s), 8.18-8.07 (4H, m), 8.02 (1H, dd, *J* = 8.0, 1.5 Hz), 7.94 (1H, d, *J* = 8.0 Hz), 7.87-7.76 (2H, m), 7.72-7.59 (2H, m), 3.36 (3H, s), 2.79 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.87, 156.84, 152.95, 150.28, 147.31, 146.12, 146.03, 143.13, 140.84, 139.31, 137.65, 130.97, 130.44, 130.08-129.82 (3C, m), 128.10, 127.60, 127.16, 125.99, 125.91, 124.21, 122.35, 121.81, 125.99, 125.91, 124.21, 122.35, 121.81, 121.07, 120.42, 119.31, 43.09, 18.39; *m/z* HRMS (ESI + APCI) found $[M+H]^+$ 562.0766, $C_{29}H_{22}Cl_2N_3O_3S^+$ requires 562.0753.

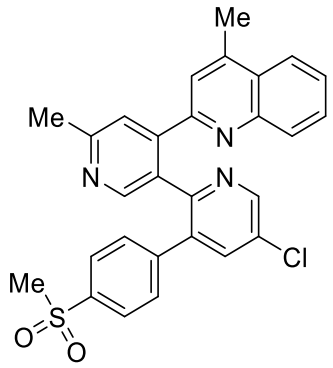
5,7-Dichloro-4'-ethoxy-4-(4-fluorophenoxy)-2,2'-biquinoline (4s)



Prepared according to general procedure C, using (5,7-dichloro-4-(4-fluorophenoxy)quinolin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (203 mg, 0.25 mmol), trifluoromethanesulfonic acid (42 μL, 0.50 mmol), and (2,2,2)-Trifluoroethanol (625 μL) at 80 °C for 36 hours. The crude material was suspended in a 5mL CH_2Cl_2 and filtered over a frit with cold CH_2Cl_2 to provide the title compound as a white crystalline solid (69 mg, 0.15 mmol, 58% yield). mp 235-238 °C; IR ν_{max}/cm^{-1} (film): 3065, 2978, 1430, 1296, 1214, 1117, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (1H, d, *J* = 8.2 Hz), 8.19-8.12 (2H, m), 8.10 (1H, s), 7.97 (1H, d, *J* = 8.4 Hz), 7.67 (1H, t, *J* = 7.3 Hz), 7.60 (1H, d, *J* =

1.8 Hz), 7.51 (1H, t, *J* = 15.0 Hz), 7.24 (4H, m), 4.47 (2H, q, *J* = 7.0 Hz), 1.64 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.60, 162.32, 159.93 (d, *J* = 243.8 Hz), 158.99, 155.89, 151.37, 150.39 (d, *J* = 2.7 Hz), 148.69, 134.94, 130.24, 129.86, 129.67, 129.42, 128.18, 126.26, 122.87 (d, *J* = 8.5 Hz), 121.94, 121.77, 118.42, 116.98 (d, *J* = 23.6 Hz), 105.31, 98.17, 64.38, 14.55; ^{19}F NMR δ: −117.56 (m); *m/z* HRMS (DART) found $[M+H]^+$ 479.0709, $C_{26}H_{18}Cl_2FN_2O_2^+$ requires 479.0724.

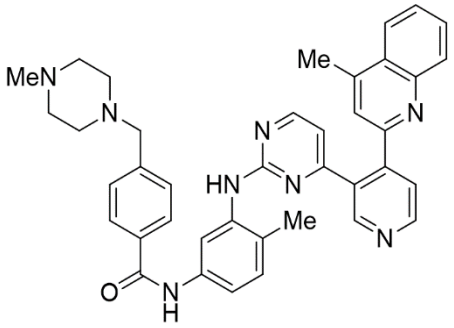
2-(5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)-4-methylquinoline (4t)



Prepared according to general procedure C, using (5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (83 mg, 0.10 mmol), trifluoromethanesulfonic acid (26 μL, 0.30 mmol), and EtOH (0.25 mL) at 80 °C for 22 hours. The crude material was purified by flash chromatography (silica gel gradient elution: 3% MeOH in CH_2Cl_2 to 4% MeOH in CH_2Cl_2) to provide the title compound as a white crystalline solid (40 mg, 0.08 mmol, 80% yield). mp 286-290 °C; IR ν_{max}/cm^{-1} (film): 3034, 2926, 1506, 1264, 1034, 873, 863; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69-8.59 (2H, m), 7.96 (1H, d, *J* = 8.0 Hz), 7.68-7.43 (6H, m), 7.35 (1H, s), 6.94-6.81 (3H, m), 3.00 (3H, s), 2.67 (3H, s), 2.61 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ:

159.16, 154.96, 154.07, 151.54, 147.94, 147.32, 147.11, 145.21, 143.07, 139.47, 136.47, 136.03, 130.77, 130.59, 130.02, 129.61, 129.56, 127.08, 126.92, 126.75, 123.57, 122.81, 120.92, 44.39, 24.42, 18.78; *m/z* HRMS (DART) found $[M+H]^+$ 500.1175, $C_{28}H_{23}ClN_3O_2S^+$ requires 500.1194.

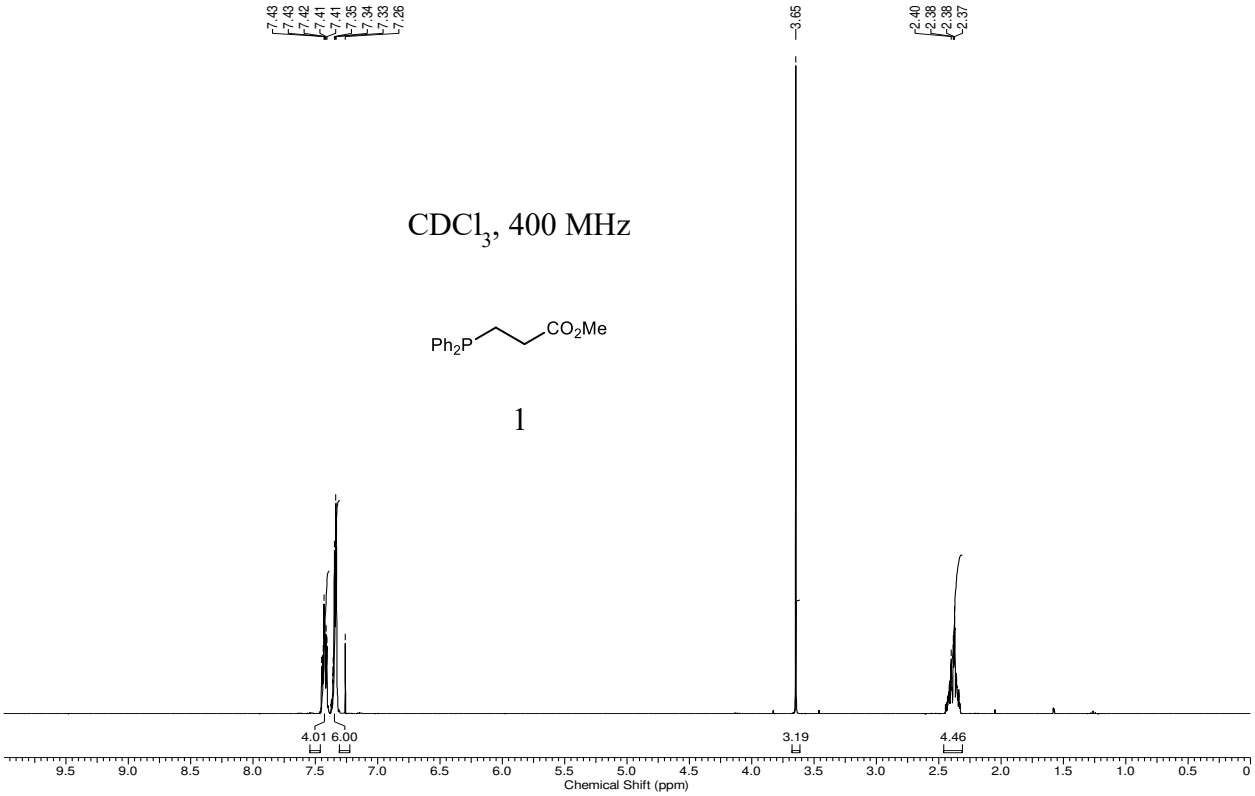
_N_-(4-Methyl-3-((4-(4-(4-methylquinolin-2-yl)pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (4u)

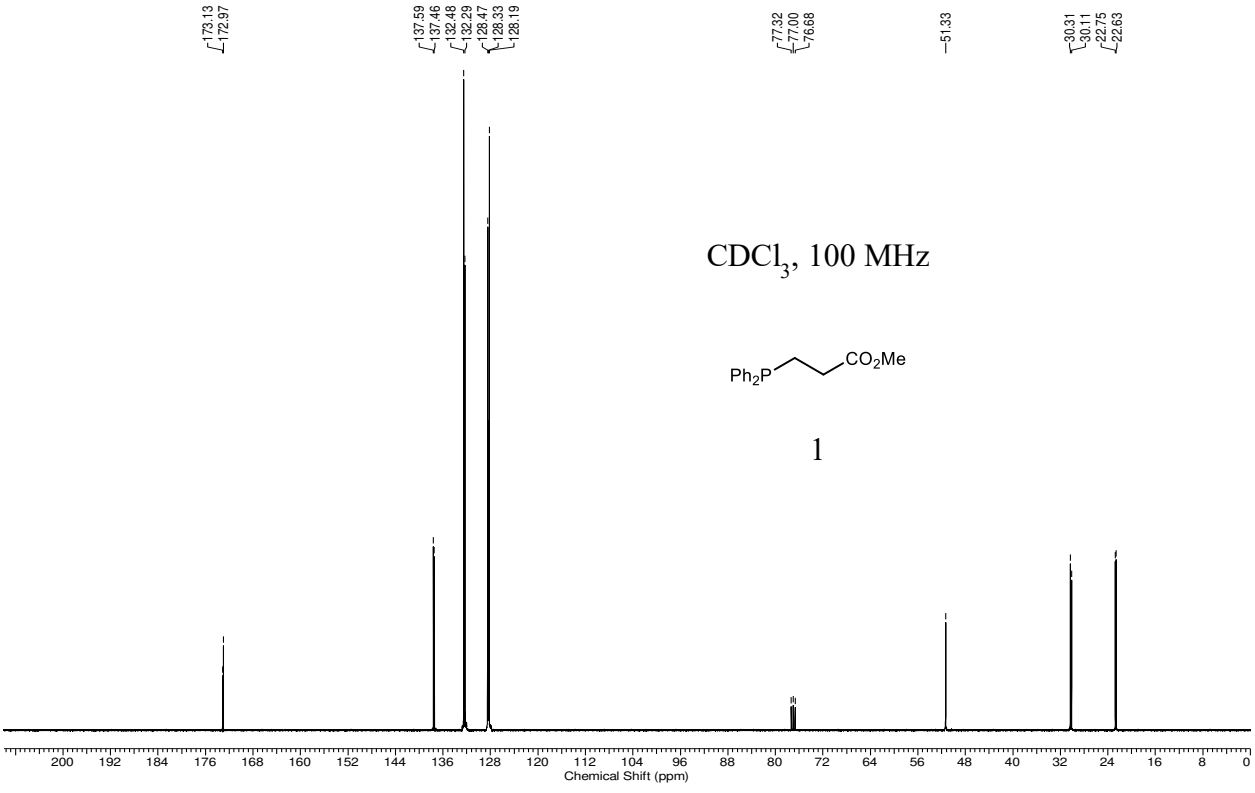


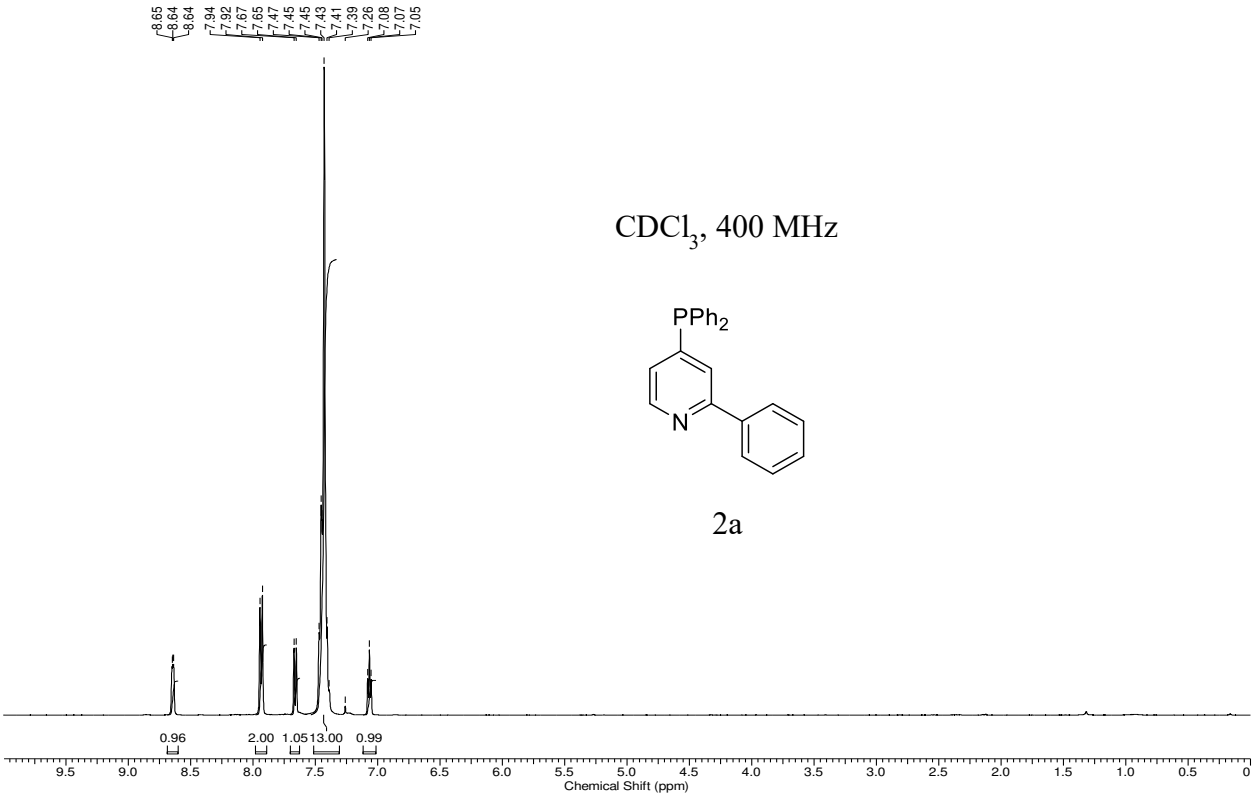
Prepared according to general procedure C using (3-(2-((2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (97 mg, 0.10 mmol), trifluoromethanesulfonic acid (36 μL, 0.40 mmol) and EtOH (0.25 mL) at 80 °C for 48 hours. Flash column chromatography by three times (silica gel: 30% toluene, 3% MeOH and 1% Et_3N in CH_2Cl_2) afforded the title compound as a colorless oil (26 mg, 0.04 mmol, 41% yield). IR υ_{max}/cm^{-1} (film): 3249, 3036, 2933, 2796, 1663, 1572, 1553, 1525, 1505, 1446, 1406, 1349, 1287, 1204, 1162, 1138, 1010, 906, 816, 758, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.02 (1H, s), 8.83 (1H, d, *J* = 5.0 Hz), 8.26 (1H, d, *J* = 5.1 Hz), 8.09 (1H, s), 7.96–7.87 (5H, m), 7.72 (1H, d, *J* = 5.0 Hz), 7.66 (1H, t, *J* = 7.5 Hz), 7.55 (1H, t, *J* = 7.4 Hz), 7.48–7.44 (3H, m), 7.09–7.06 (2H, m), 6.83 (1H, s), 6.62 (1H, d, *J* = 5.1 Hz), 3.56 (2H, s), 2.57–2.29 (14H, m), 2.13 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.33, 164.51, 160.07, 157.95, 156.20, 150.85, 150.62, 147.78, 147.57, 144.55, 142.50, 137.36, 136.47, 133.86, 132.78, 130.60, 129.99, 129.67, 129.24, 127.14, 127.12, 126.91, 124.53,

123.66, 123.51, 122.41, 115.13, 112.72, 112.53, 62.52, 55.08, 53.12, 45.99, 18.74, 17.32; *m/z* HRMS (ESI + APCI) found $[M+H]^+$ 635.3221, $C_{39}H_{39}N_8O^+$ requires 635.3247.

A 2.4 Spectra

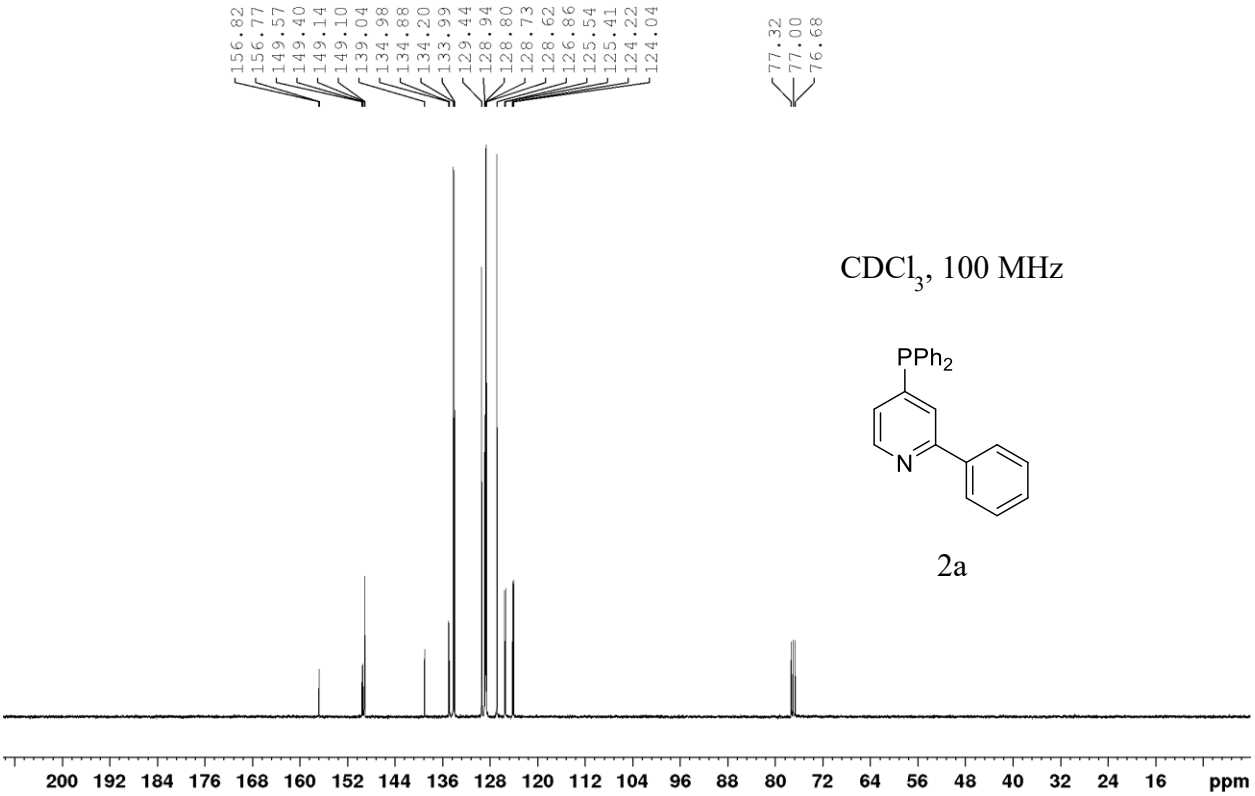

7.43
7.43
7.42
7.41
7.41
7.35
7.34
7.33
7.26
3.65
2.40
2.38
2.38
2.37
CDCl3, 400 MHz
Ph2P
CO2Me
1
4.01
6.00
3.19
4.46
Chemical Shift (ppm)


173.13
172.97
137.59
137.46
132.48
132.29
128.47
128.33
128.19
77.32
77.00
76.68
51.33
30.31
30.11
22.75
22.63
CDCl3, 100 MHz
Ph2P
CO2Me
1
Chemical Shift (ppm)



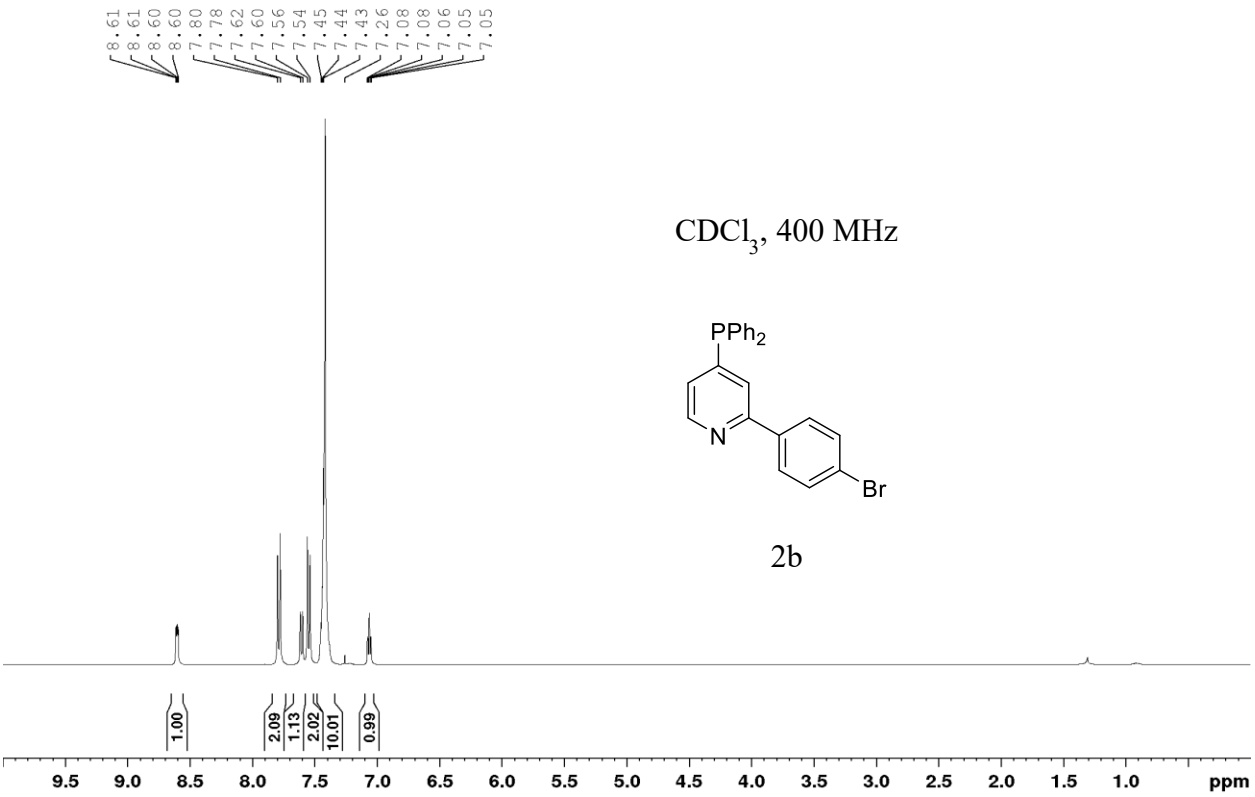
$CDCl_3$, 400 MHz

2a



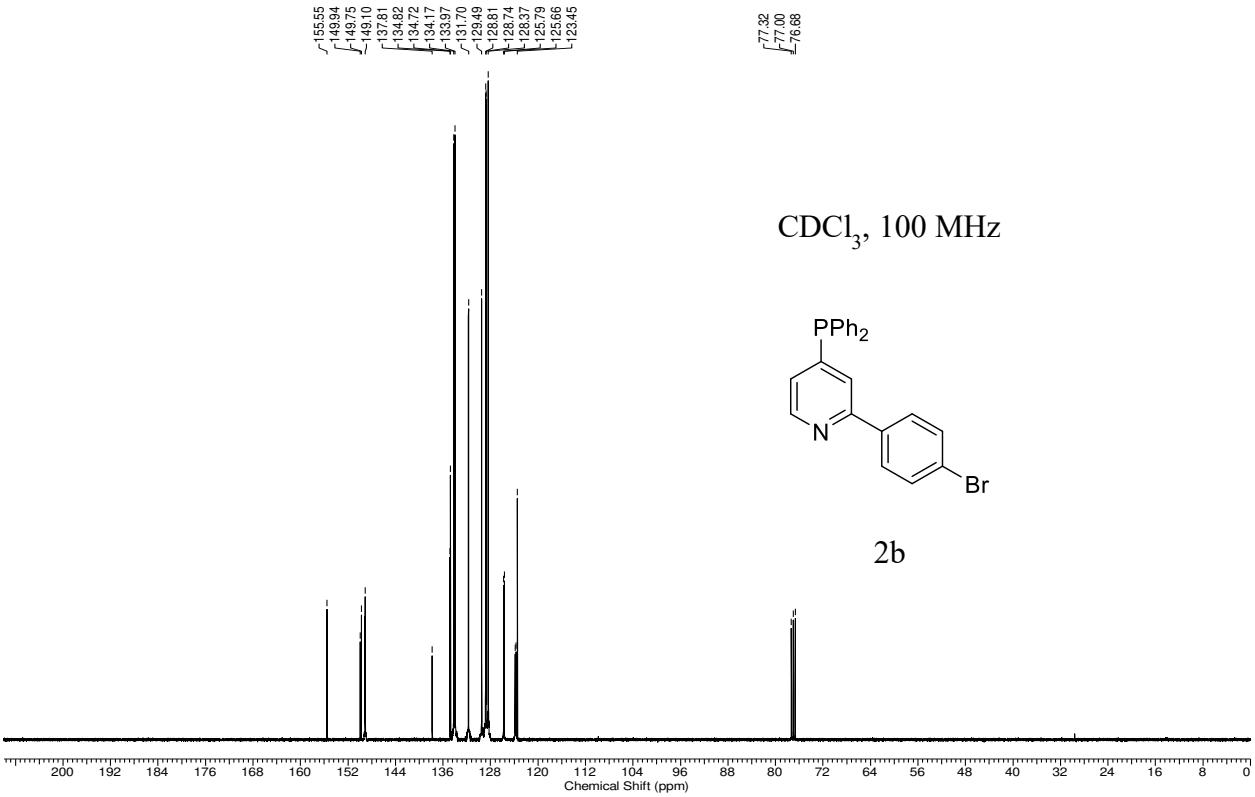
$CDCl_3$, 100 MHz

2a



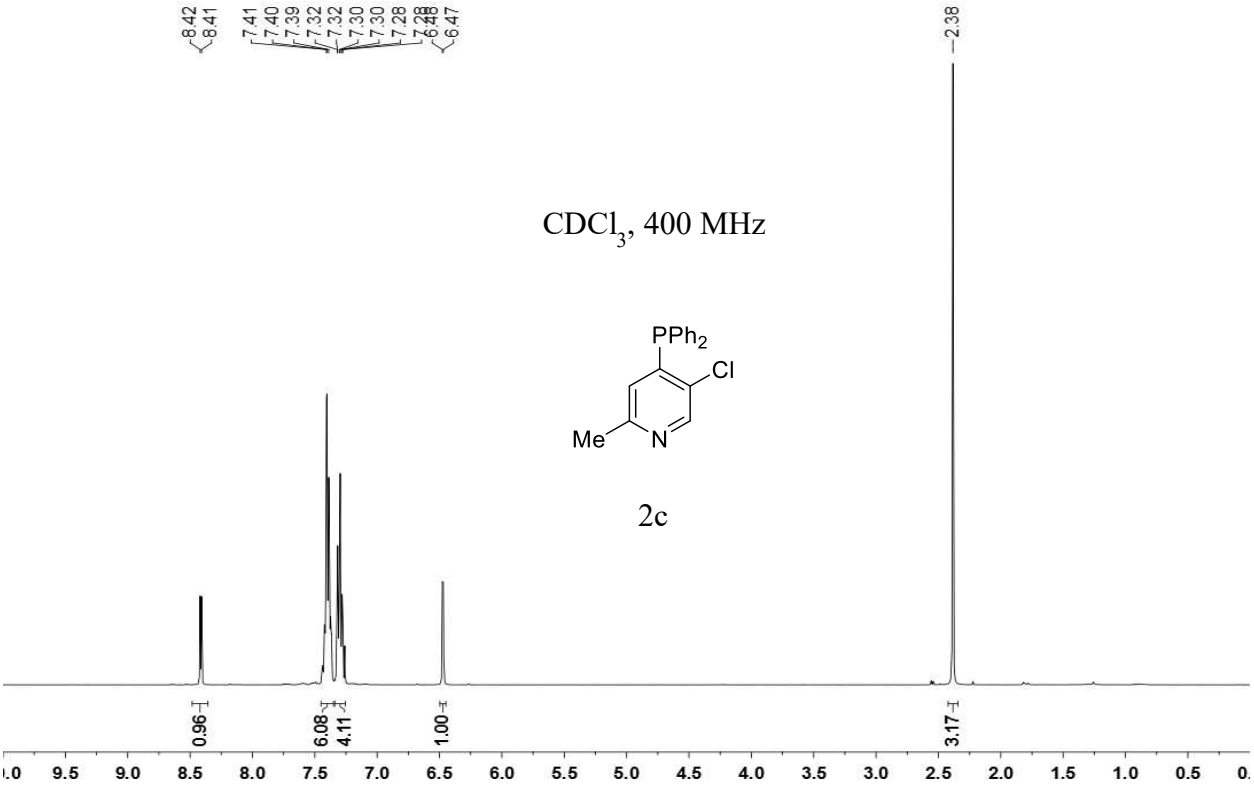
$CDCl_3$, 400 MHz

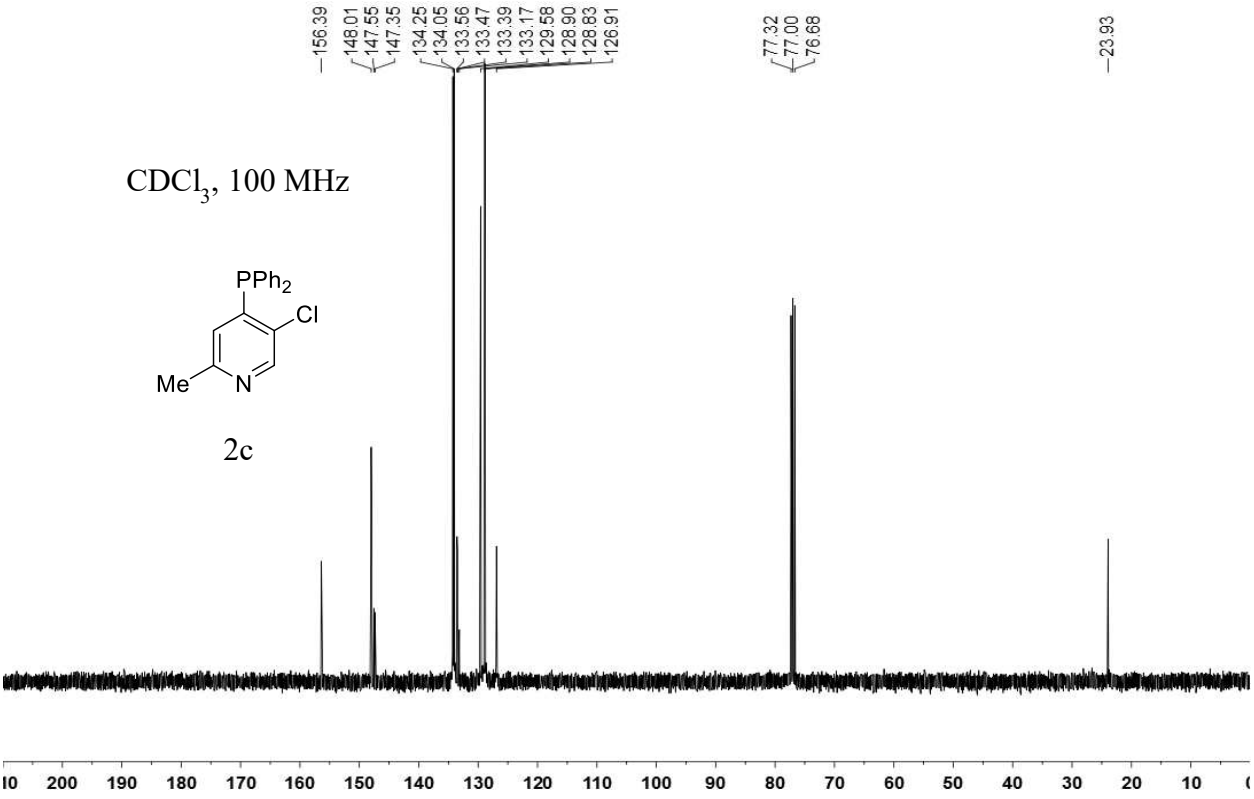
2b

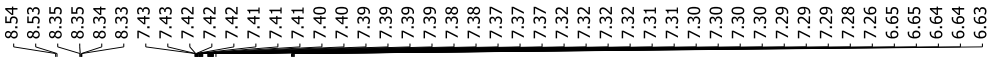


$CDCl_3$, 100 MHz

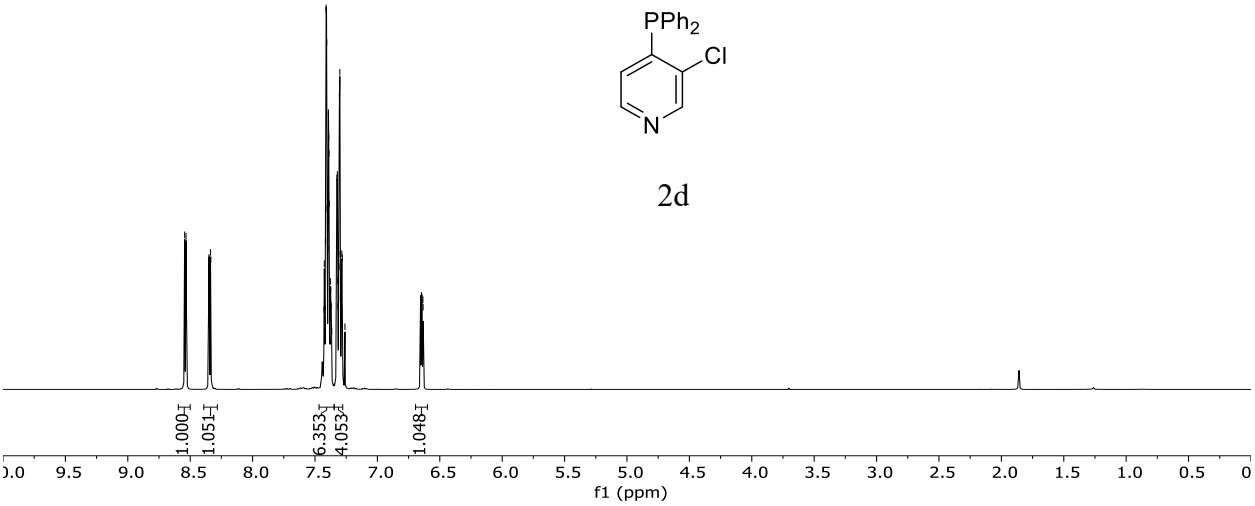
2b


8.42
8.41
7.41
7.40
7.39
7.32
7.32
7.30
7.30
7.28
6.47
2.38
CDCl3, 400 MHz
PPh2
Cl
Me
N
2c
0.96
6.08
4.11
1.00
3.17

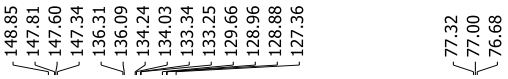

156.39
148.01
147.55
147.35
134.25
134.05
133.56
133.47
133.39
133.17
129.58
128.90
128.83
126.91
77.32
77.00
76.68
23.93
CDCl3, 100 MHz
PPh2
Cl
Me
N
2c



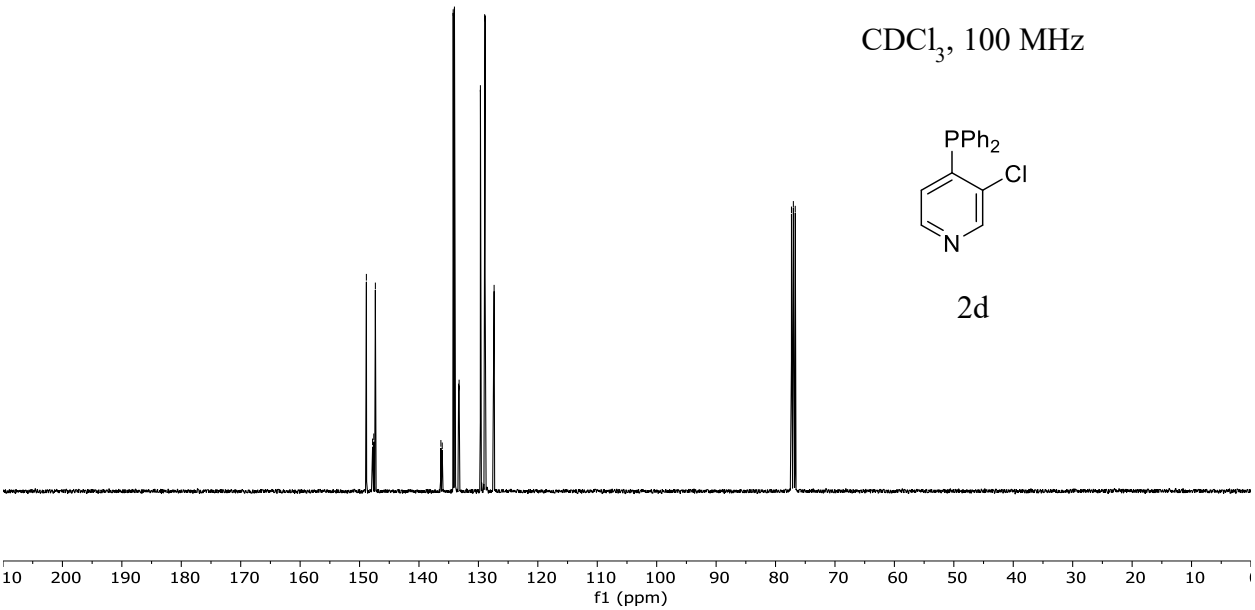
$CDCl_3$, 400 MHz



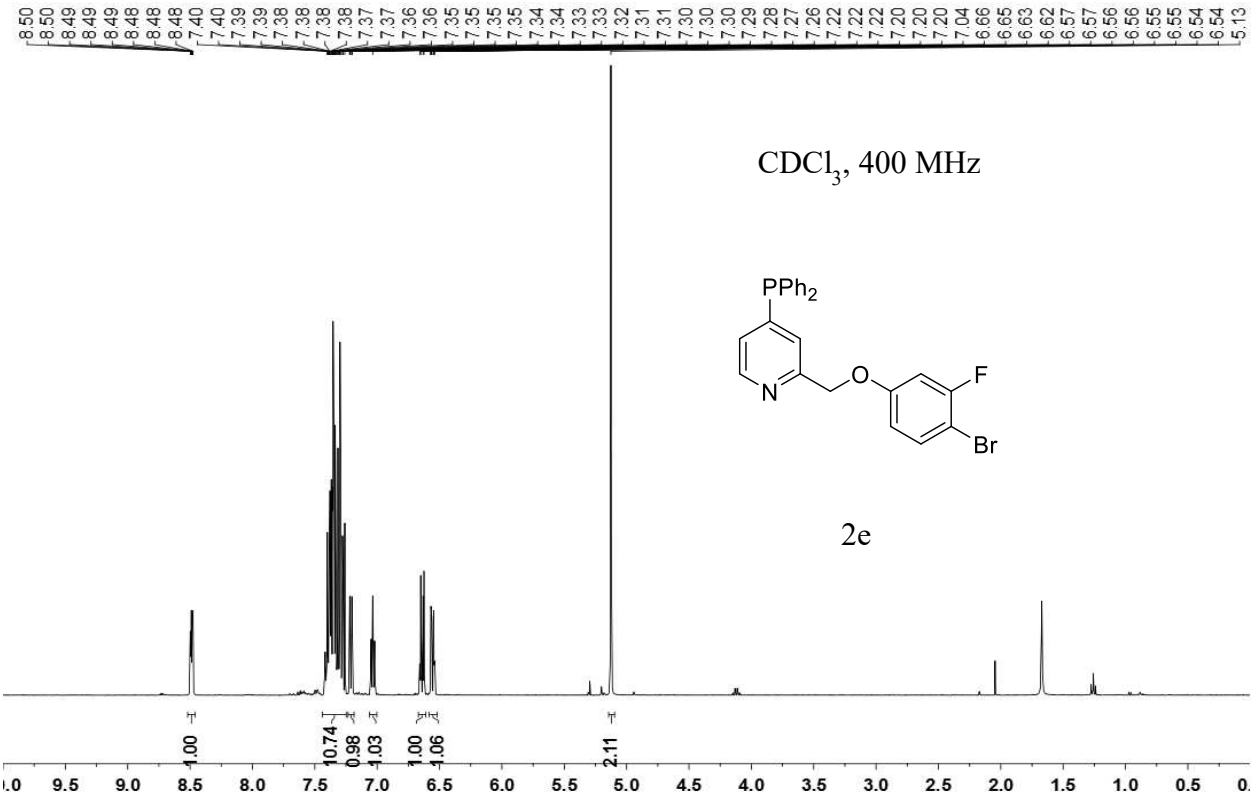
2d

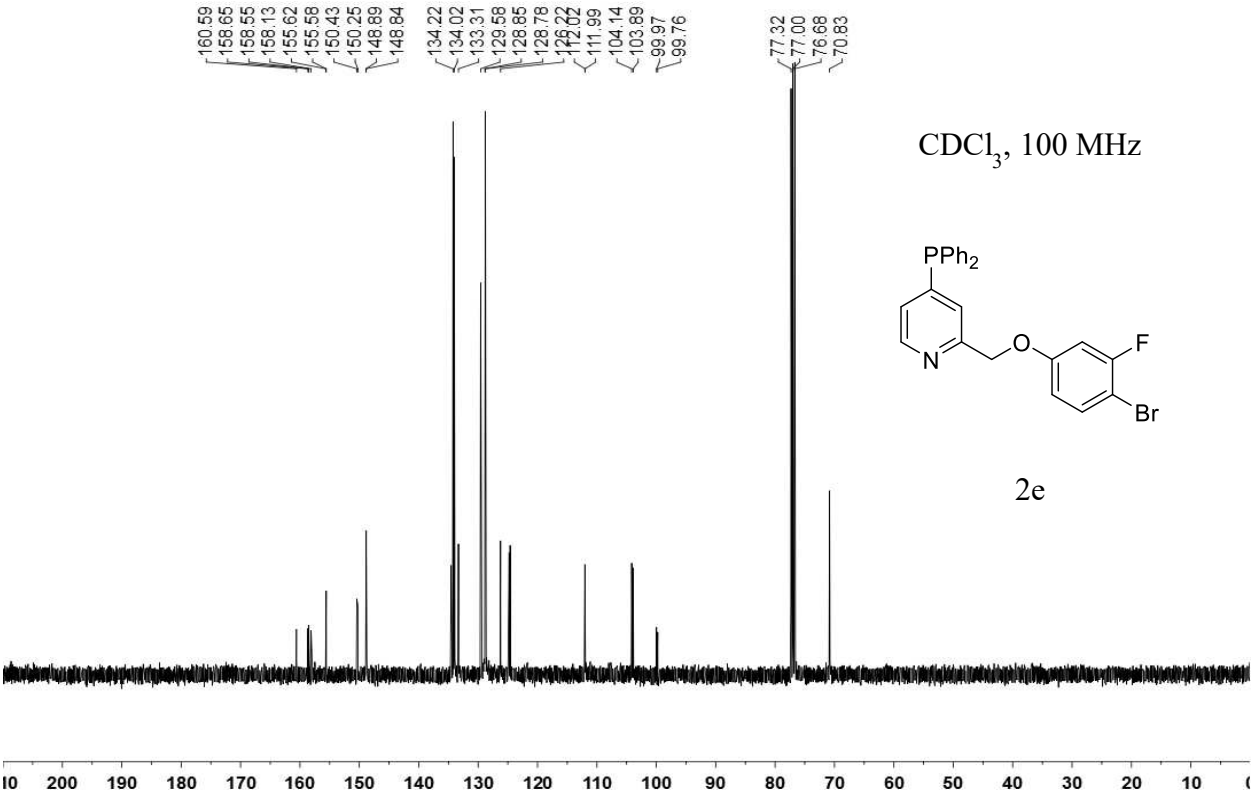


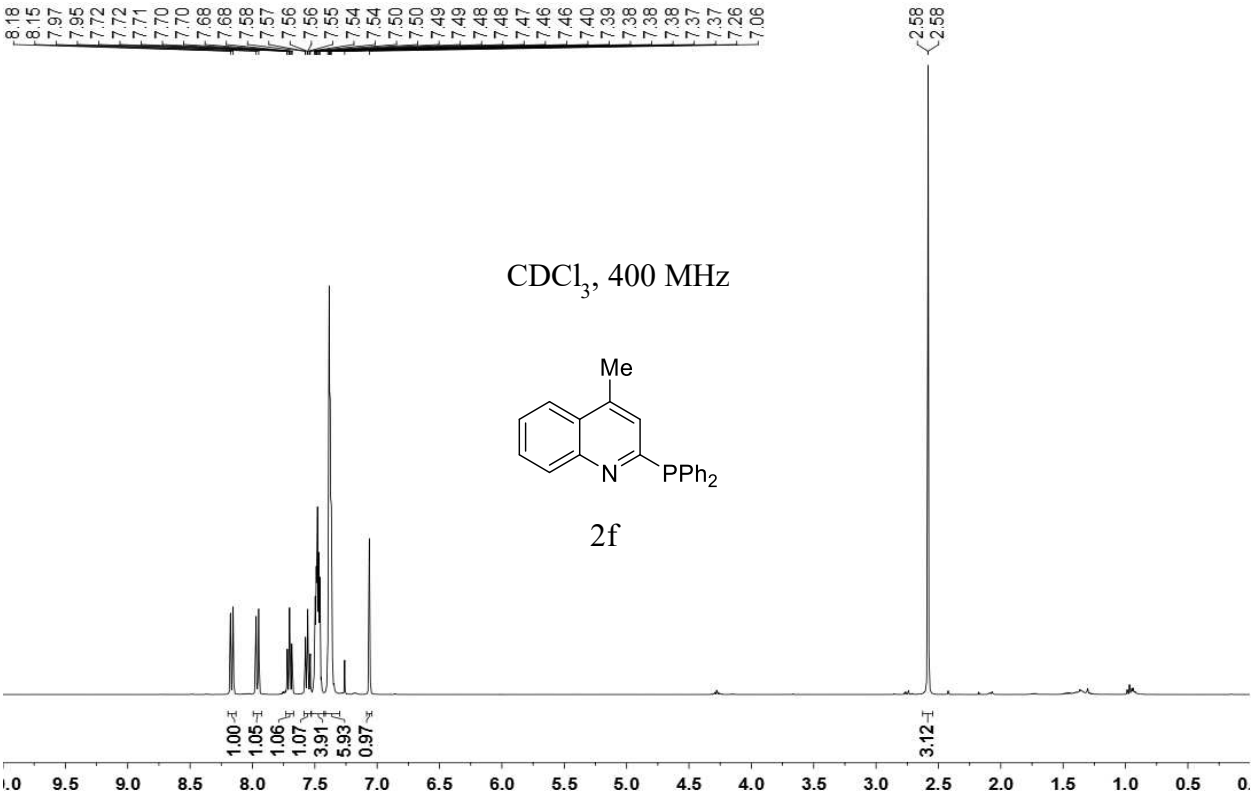
$CDCl_3$, 100 MHz

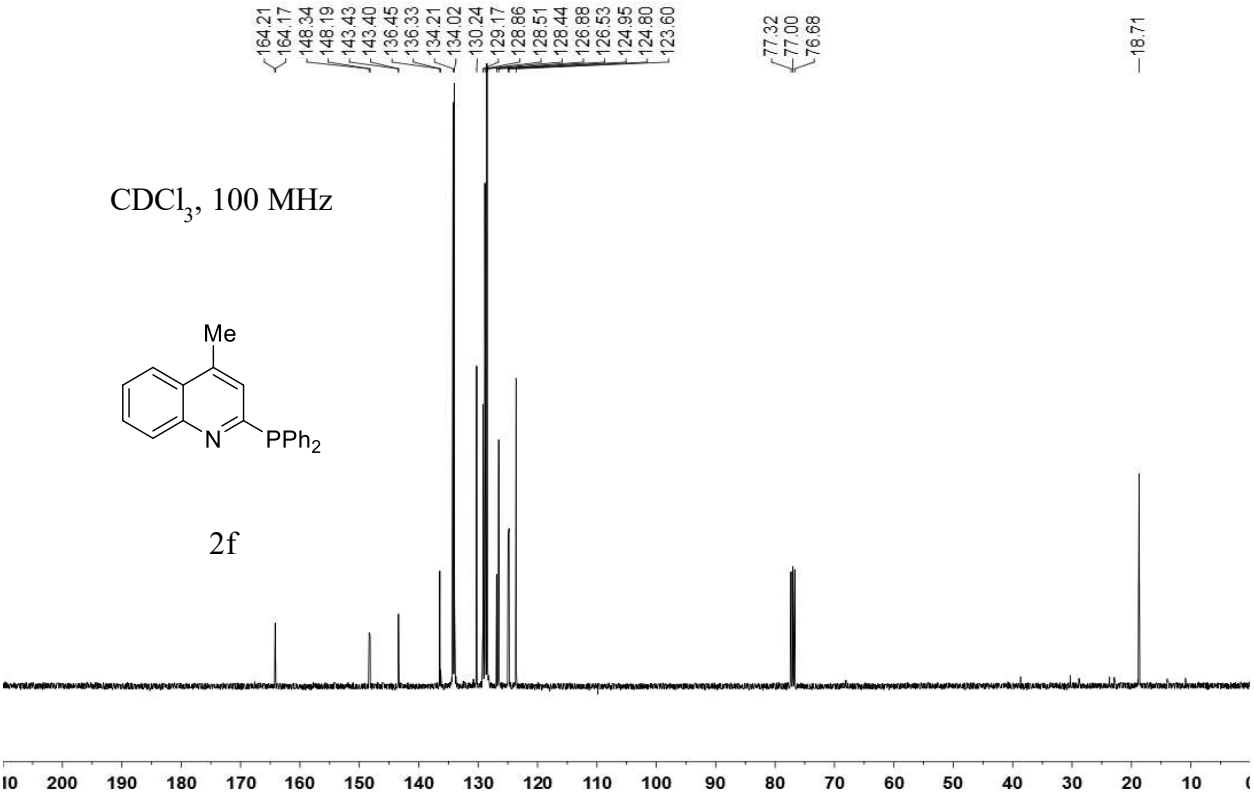


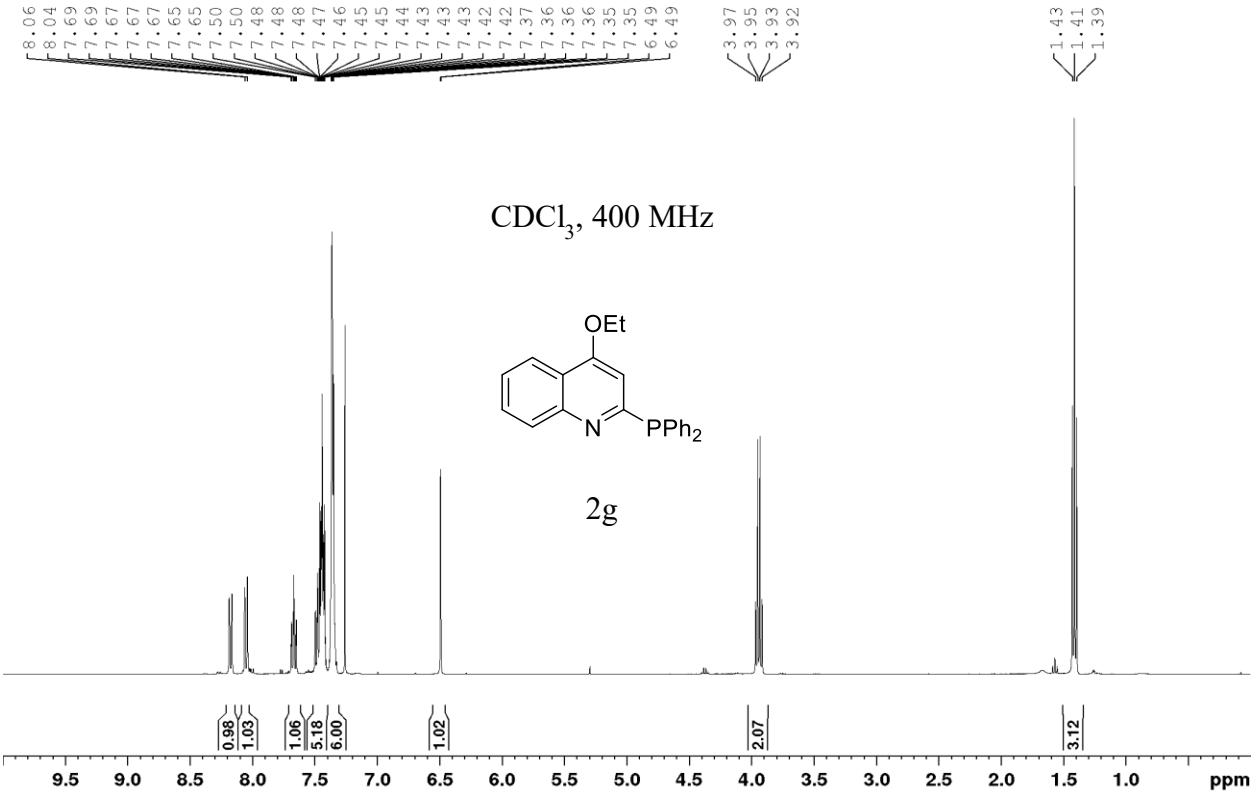
2d

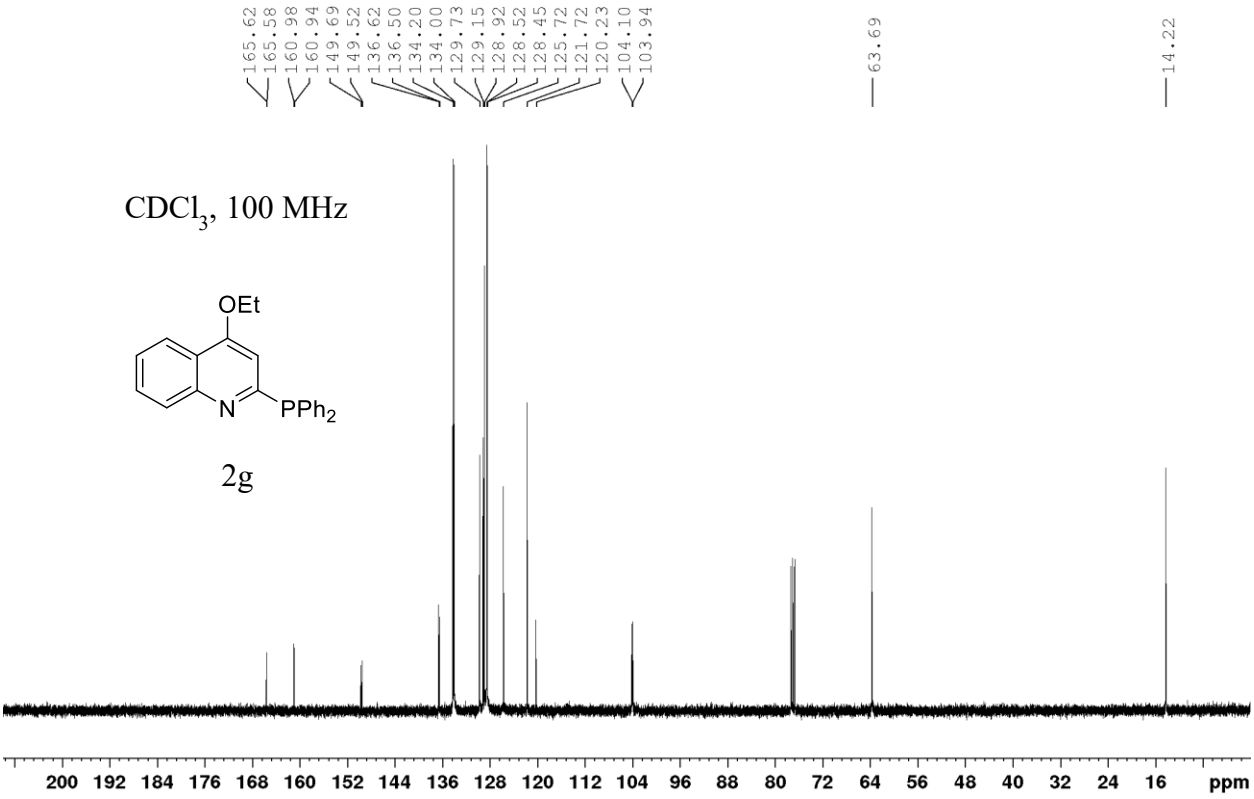

CDCl3, 400 MHz
PPh2
N
O
F
Br
2e

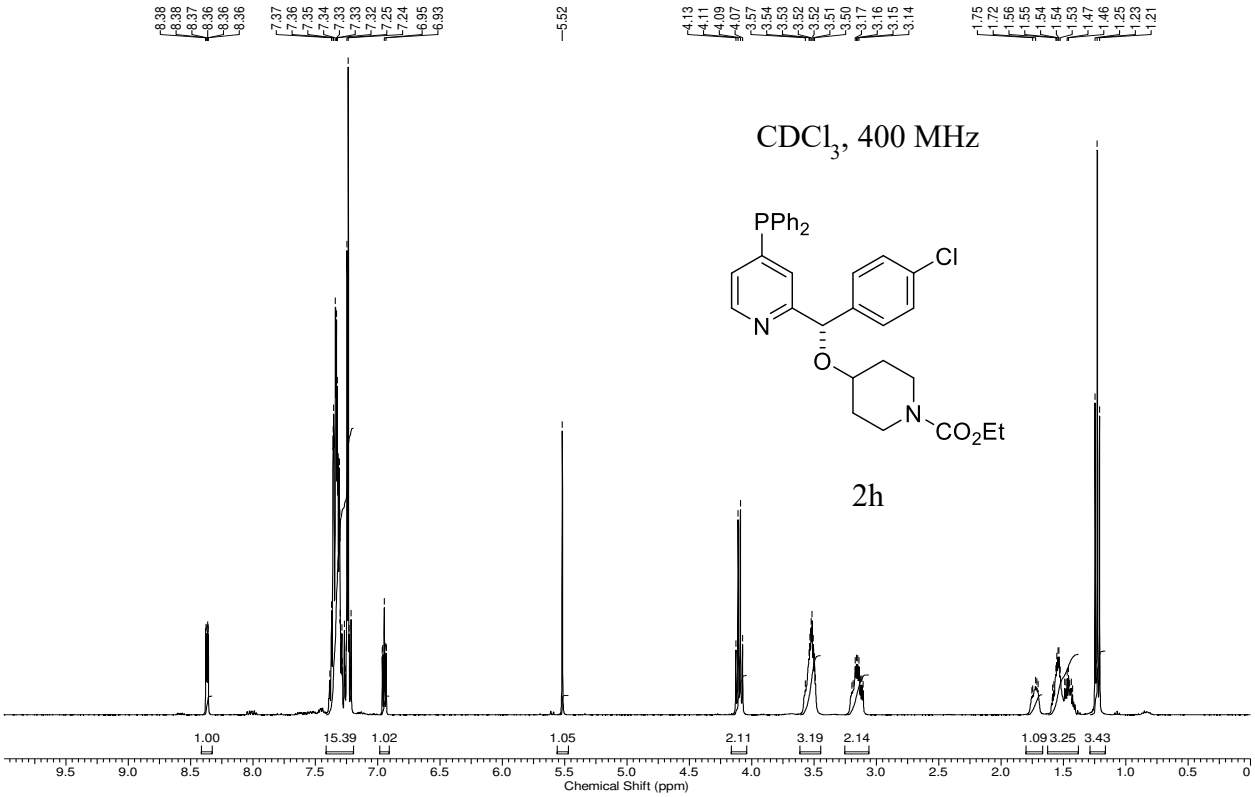

CDCl3, 100 MHz
PPh2
N
O
F
Br
2e

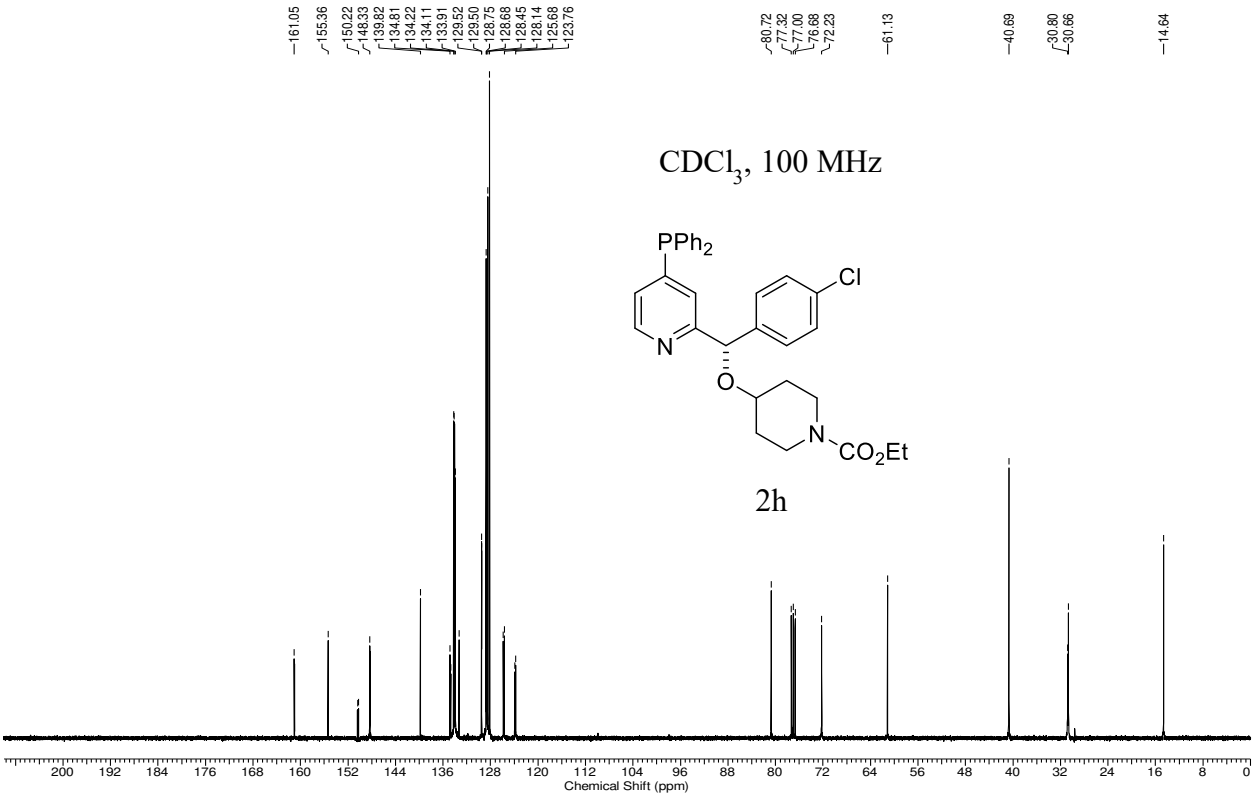

8.18
8.15
7.97
7.95
7.72
7.72
7.71
7.70
7.70
7.68
7.68
7.58
7.57
7.56
7.56
7.55
7.54
7.54
7.50
7.50
7.49
7.49
7.48
7.48
7.47
7.46
7.46
7.40
7.39
7.38
7.38
7.38
7.37
7.37
7.26
7.06
2.58
2.58
CDCl3, 400 MHz
Me
N
PPh2
2f
1.00
1.05
1.06
1.07
3.91
5.93
0.97
3.12
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

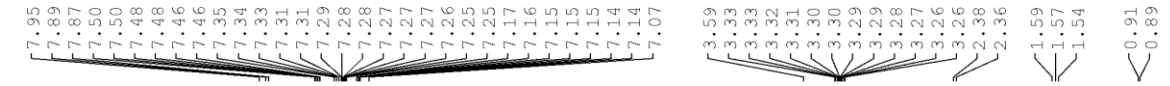

164.21
164.17
148.34
148.19
143.43
143.40
136.45
136.33
134.21
134.02
130.24
129.17
128.86
128.51
128.44
126.88
126.53
124.95
124.80
123.60
77.32
77.00
76.68
18.71
CDCl3, 100 MHz
Me
N
PPh2
2f
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


8.06
8.04
7.69
7.69
7.67
7.67
7.67
7.65
7.65
7.50
7.50
7.48
7.48
7.48
7.47
7.46
7.45
7.45
7.44
7.43
7.43
7.43
7.43
7.42
7.42
7.37
7.36
7.36
7.36
7.35
7.35
6.49
6.49
3.97
3.95
3.93
3.92
1.43
1.41
1.39
CDCl3, 400 MHz
OEt
N
PPh2
2g
0.98
1.03
1.06
5.18
6.00
1.02
2.07
3.12
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

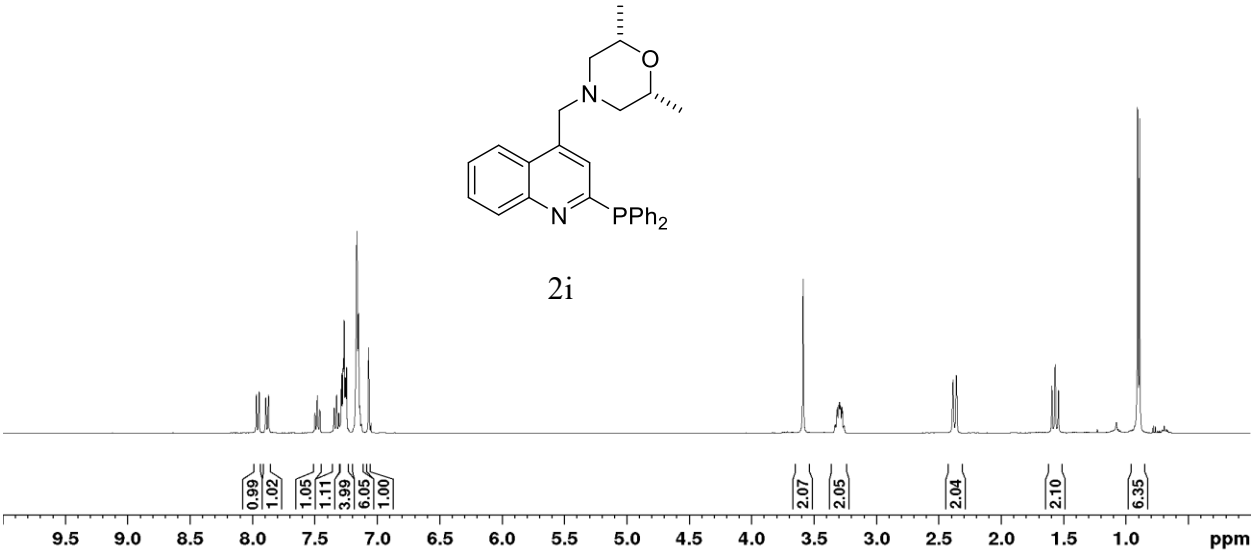

165.62
165.58
160.98
160.94
149.69
149.52
136.62
136.50
134.20
134.00
129.73
129.15
128.92
128.52
128.45
125.72
121.72
120.23
104.10
103.94
63.69
14.22
CDCl3, 100 MHz
OEt
N
PPh2
2g
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16
ppm


8.38
8.38
8.37
8.36
8.36
8.36
7.37
7.36
7.35
7.34
7.33
7.33
7.32
7.25
7.24
6.95
6.93
5.52
4.13
4.11
4.09
4.07
3.57
3.54
3.53
3.52
3.52
3.51
3.50
3.17
3.16
3.15
3.14
1.75
1.72
1.56
1.55
1.54
1.54
1.53
1.47
1.46
1.25
1.23
1.21
CDCl3, 400 MHz
PPh2
Cl
N
O
N
CO2Et
2h
1.00
15.39
1.02
1.05
2.11
3.19
2.14
1.09
3.25
3.43
Chemical Shift (ppm)

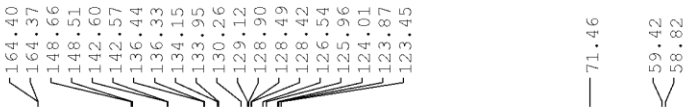

161.05
155.36
150.22
148.33
139.82
134.81
134.22
134.11
133.91
129.52
129.50
128.75
128.68
128.45
128.14
125.68
123.76
80.72
77.32
77.00
76.68
72.23
61.13
40.69
30.80
30.66
14.64
CDCl3, 100 MHz
PPh2
Cl
N
O
N
CO2Et
2h
Chemical Shift (ppm)



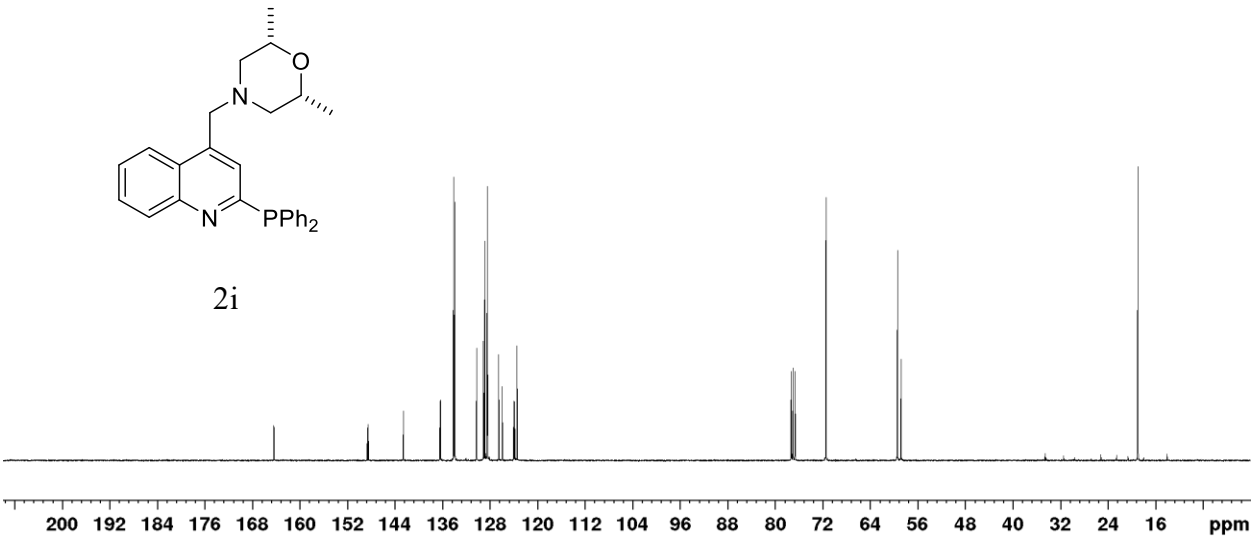
$CDCl_3$, 400 MHz



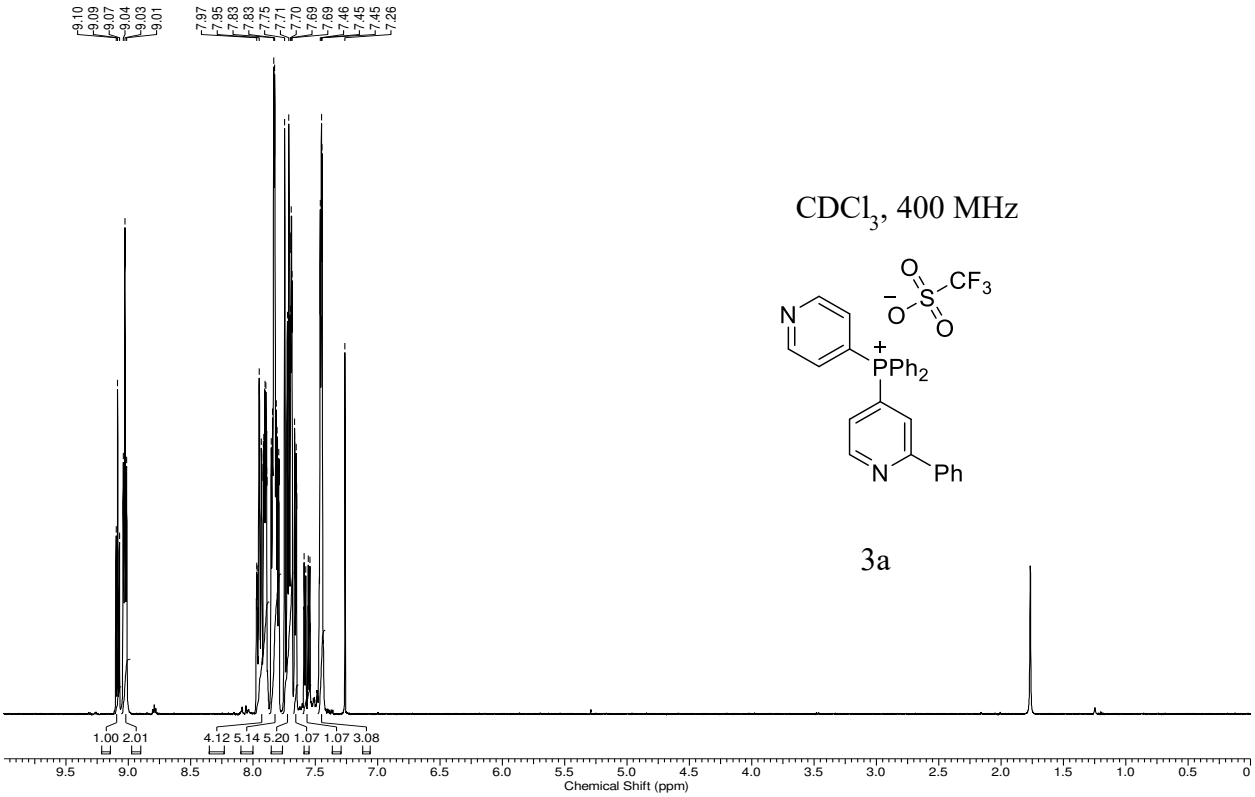
2i



$CDCl_3$, 100 MHz

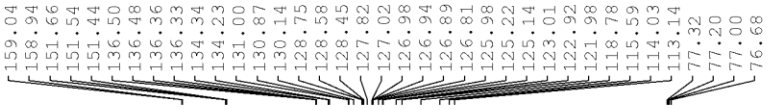


2i

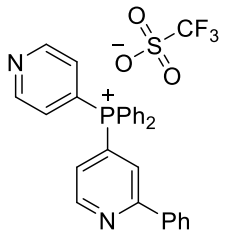


$CDCl_3$, 400 MHz

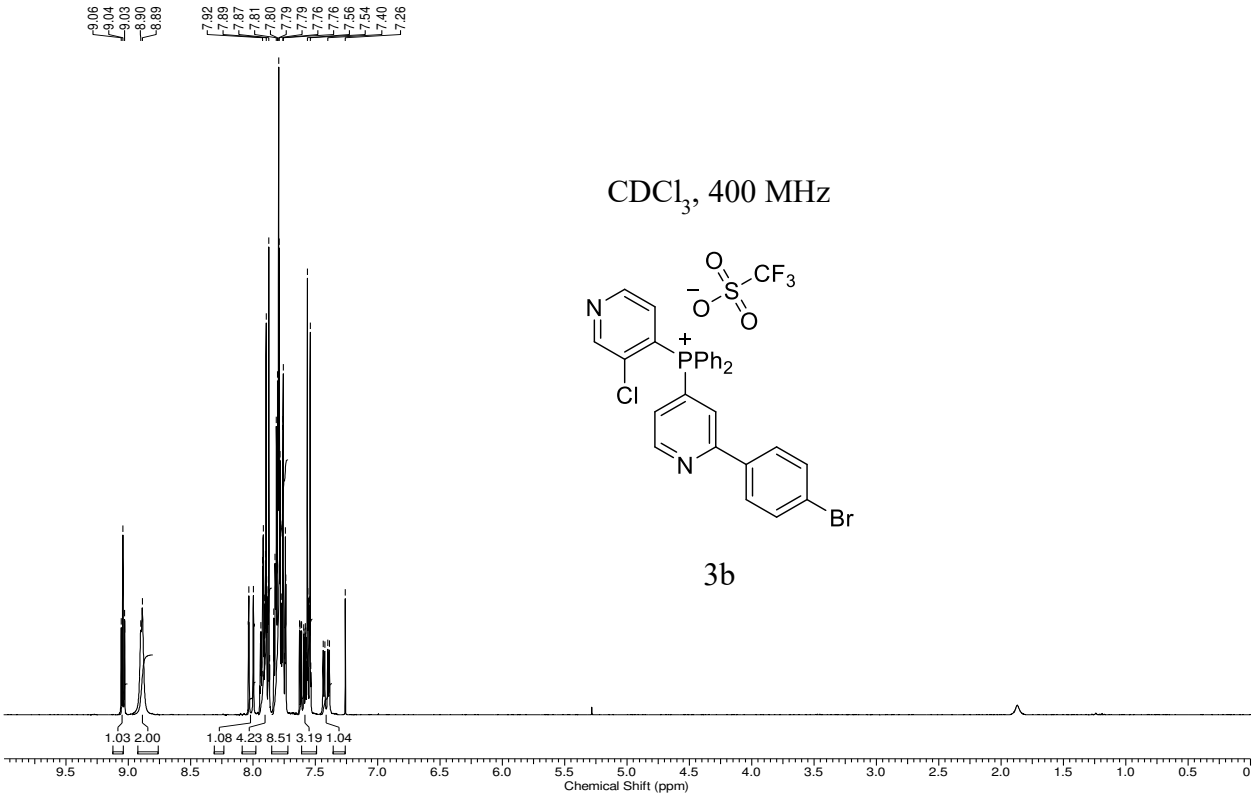
3a



$CDCl_3$, 100 MHz

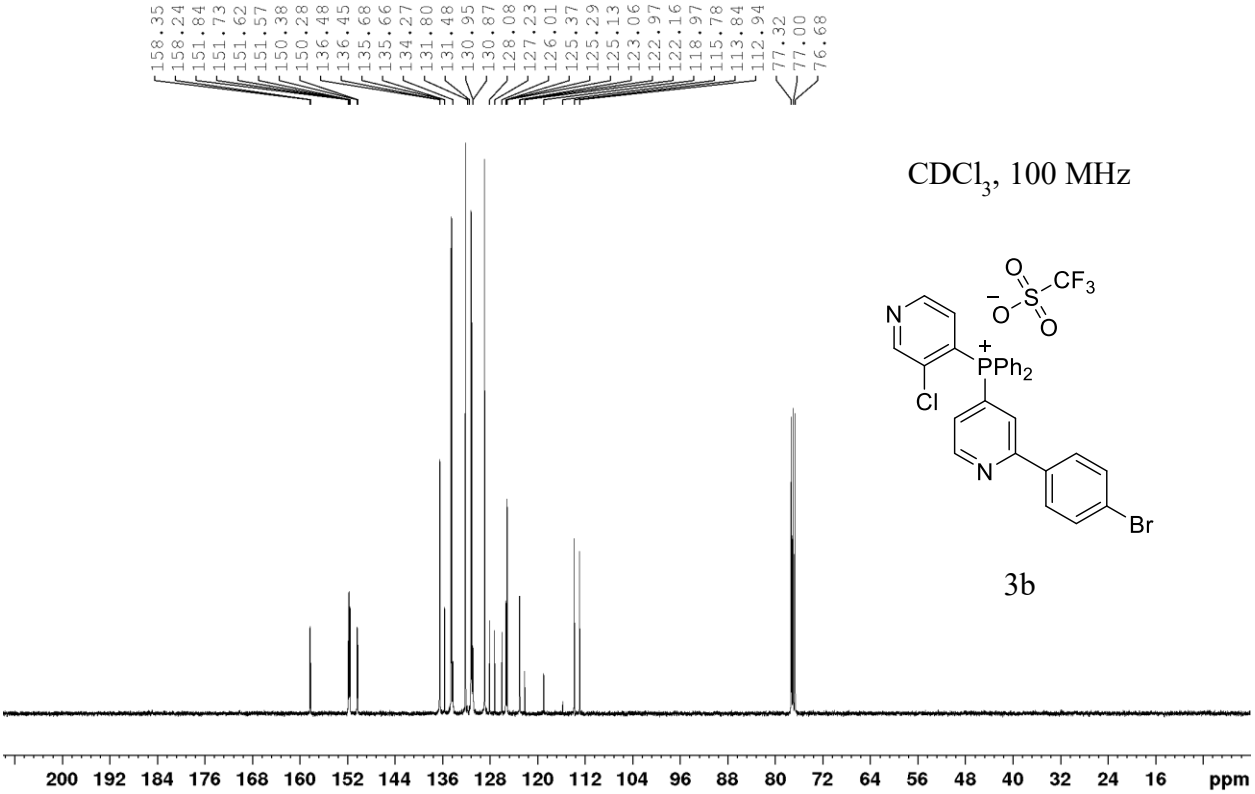


3a



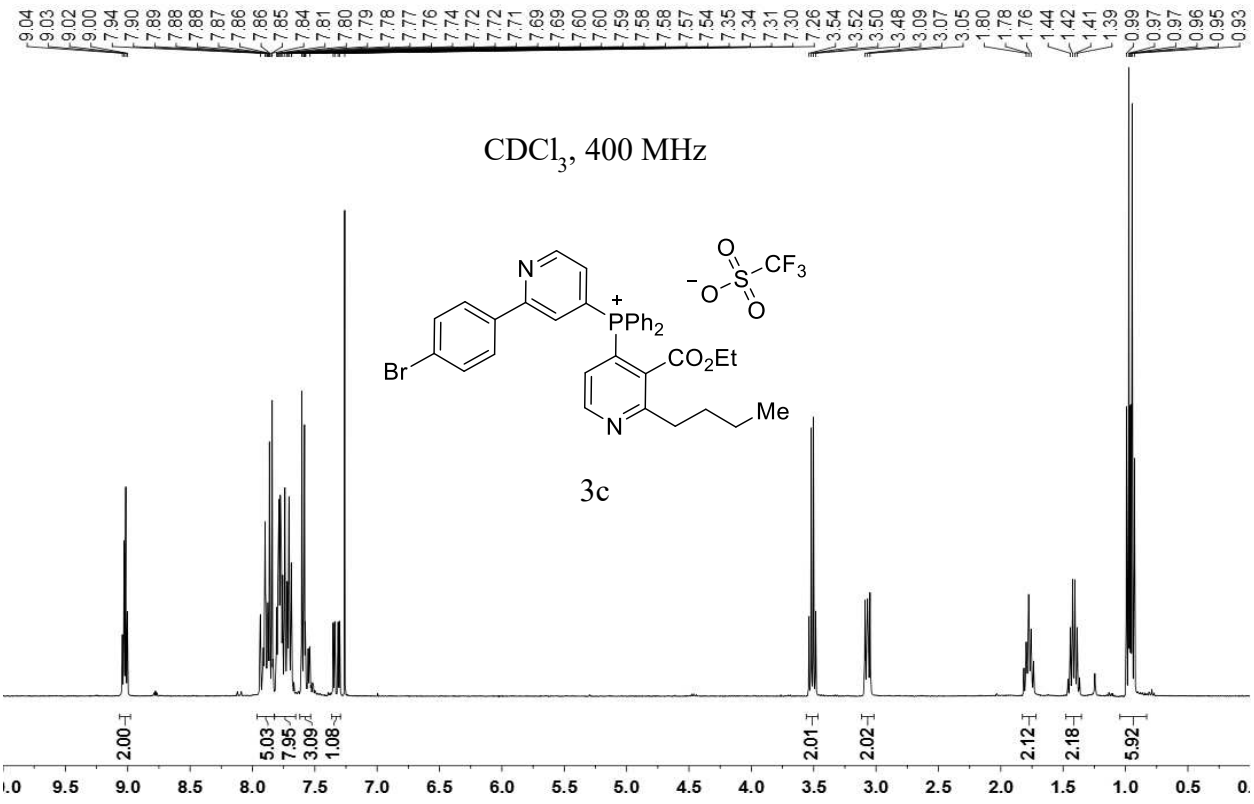
$CDCl_3$, 400 MHz

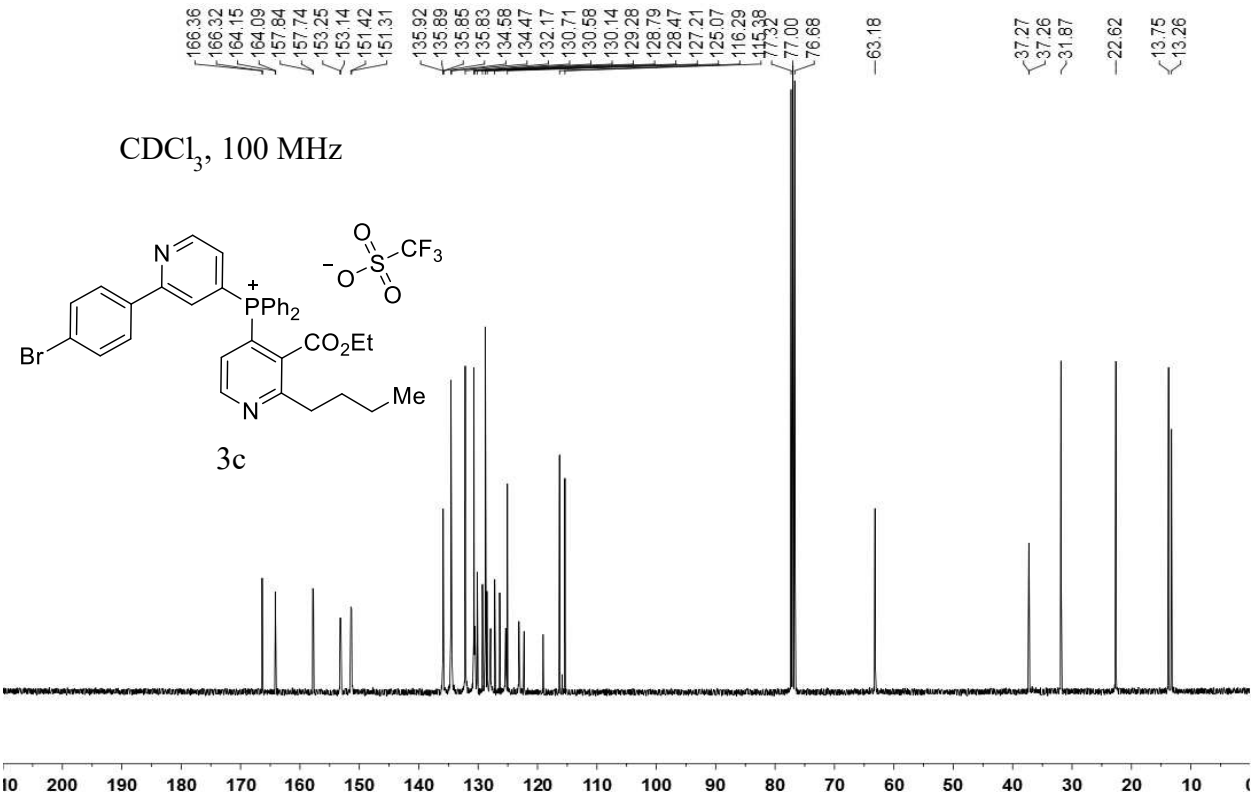
3b

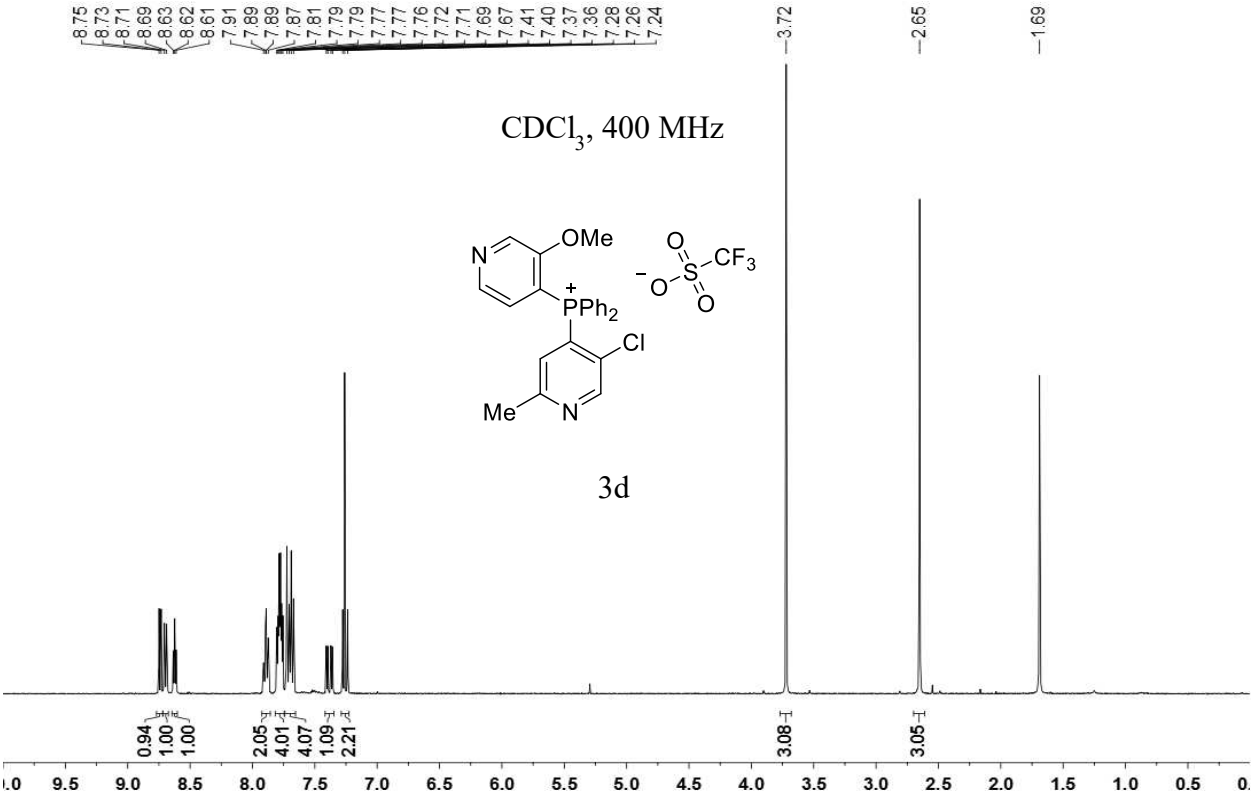


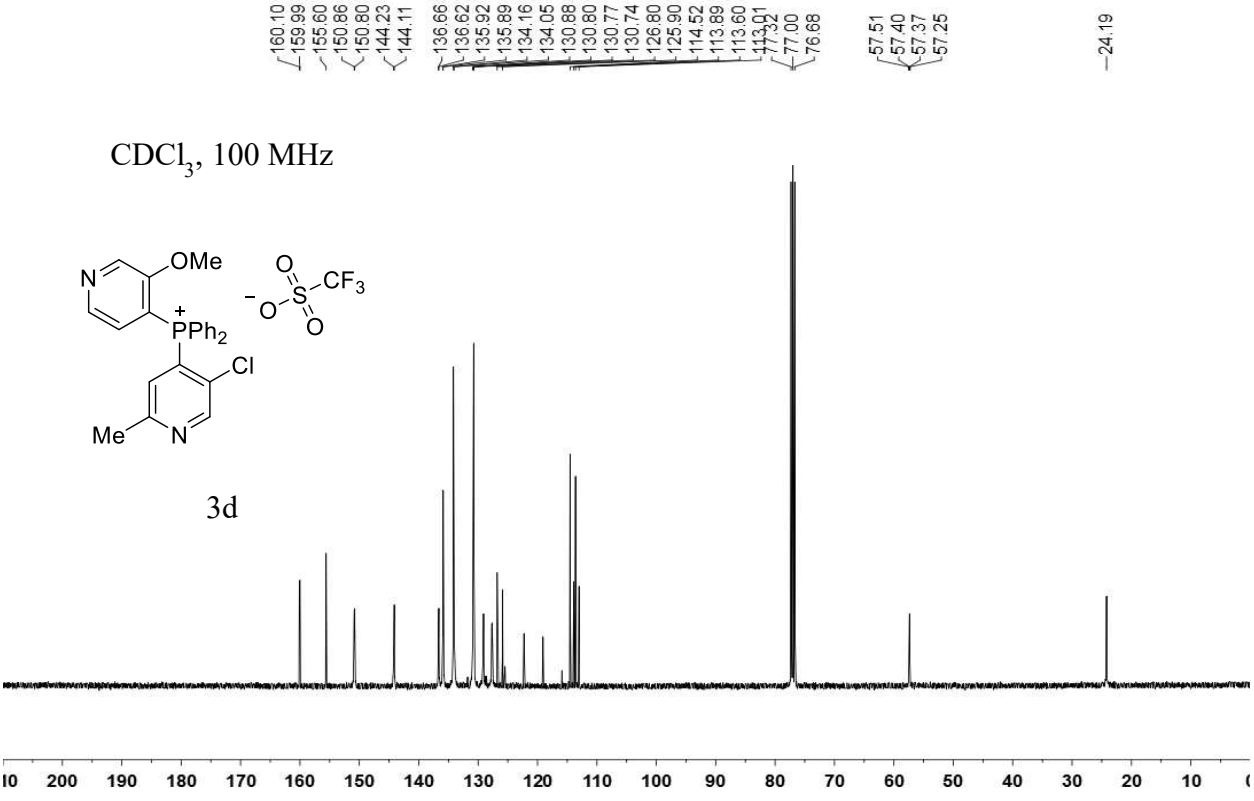
$CDCl_3$, 100 MHz

3b

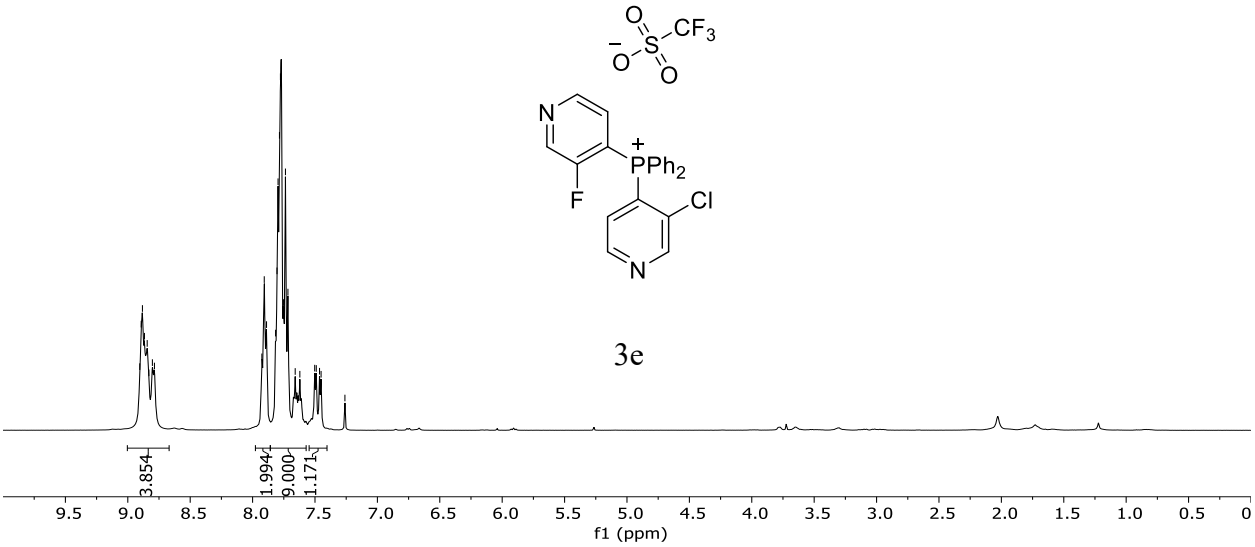

CDCl3, 400 MHz
3c

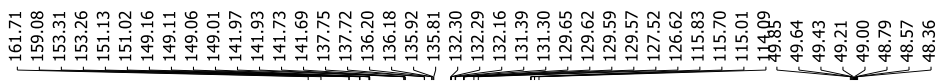

CDCl3, 100 MHz
3c


8.75
8.73
8.71
8.69
8.63
8.62
8.61
7.91
7.89
7.89
7.87
7.81
7.79
7.79
7.77
7.77
7.76
7.72
7.71
7.69
7.67
7.41
7.40
7.37
7.36
7.28
7.26
7.24
3.72
2.65
1.69
CDCl3, 400 MHz
OMe
N
PPh2
Cl
Me
N
O
S
CF3
O
O
O
3d
0.94
1.00
1.00
2.05
4.01
4.07
1.09
2.21
3.08
3.05

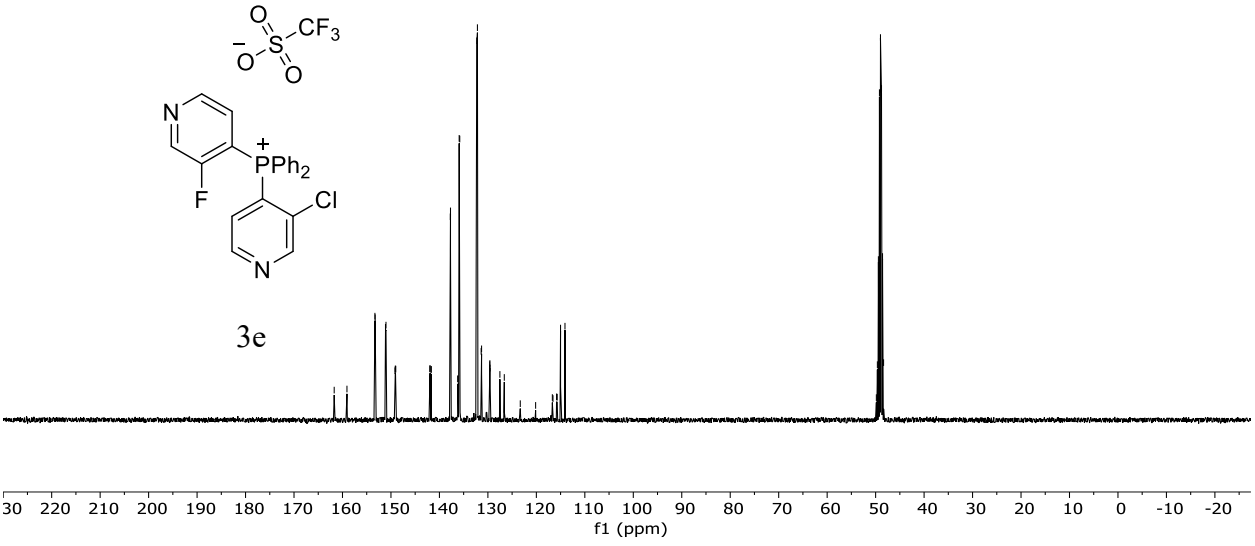

160.10
159.99
155.60
150.86
150.80
144.23
144.11
136.66
136.62
135.92
135.89
134.16
134.05
130.88
130.80
130.77
130.74
126.80
125.90
114.52
113.89
113.60
113.01
77.32
77.00
76.68
57.51
57.40
57.37
57.25
24.19
CDCl3, 100 MHz
OMe
N
PPh2
Cl
Me
N
O
S
CF3
O
O
O
3d

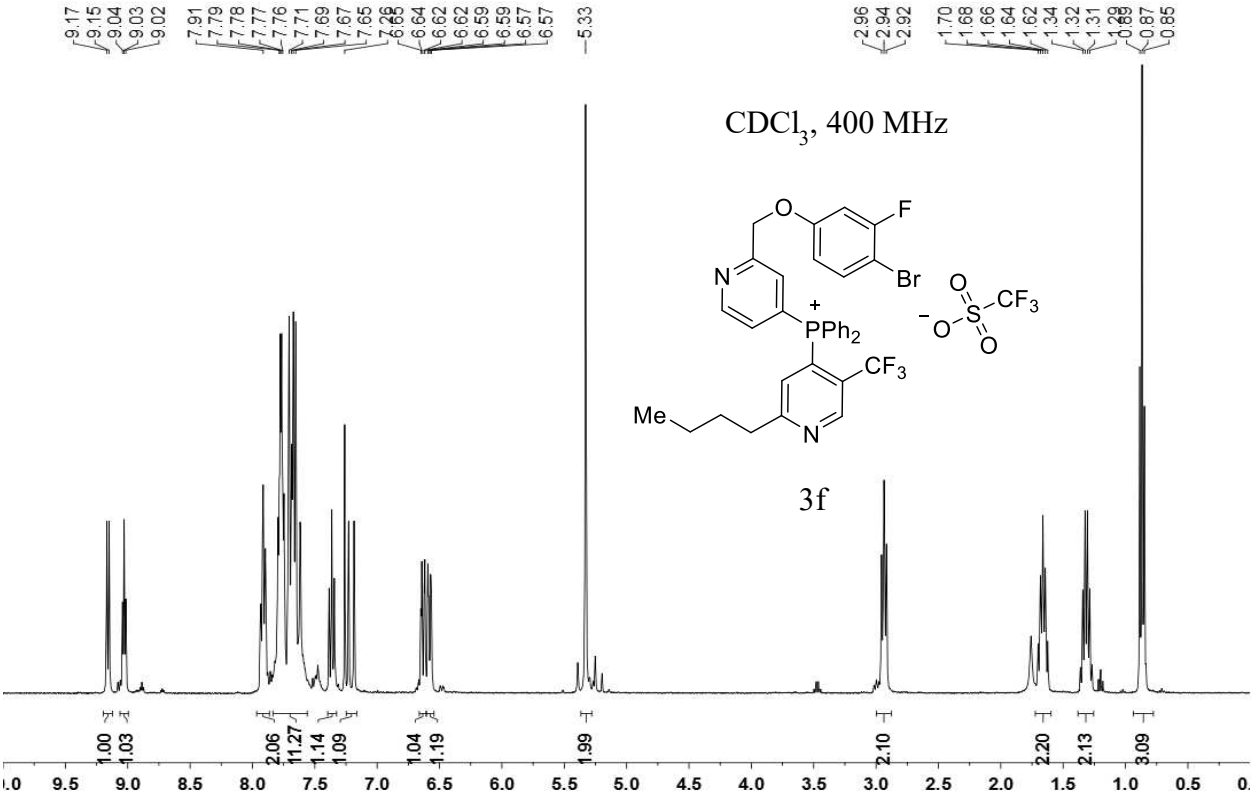
$CDCl_3$, 400 MHz

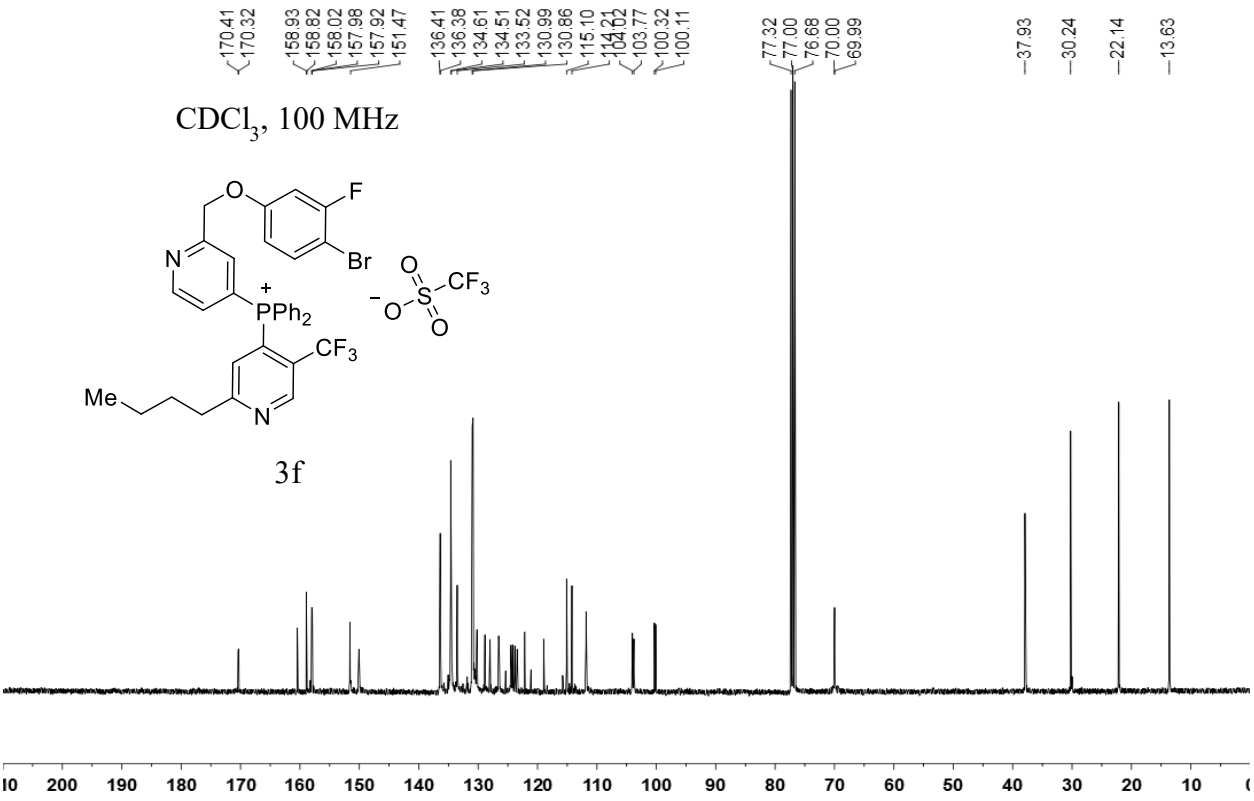


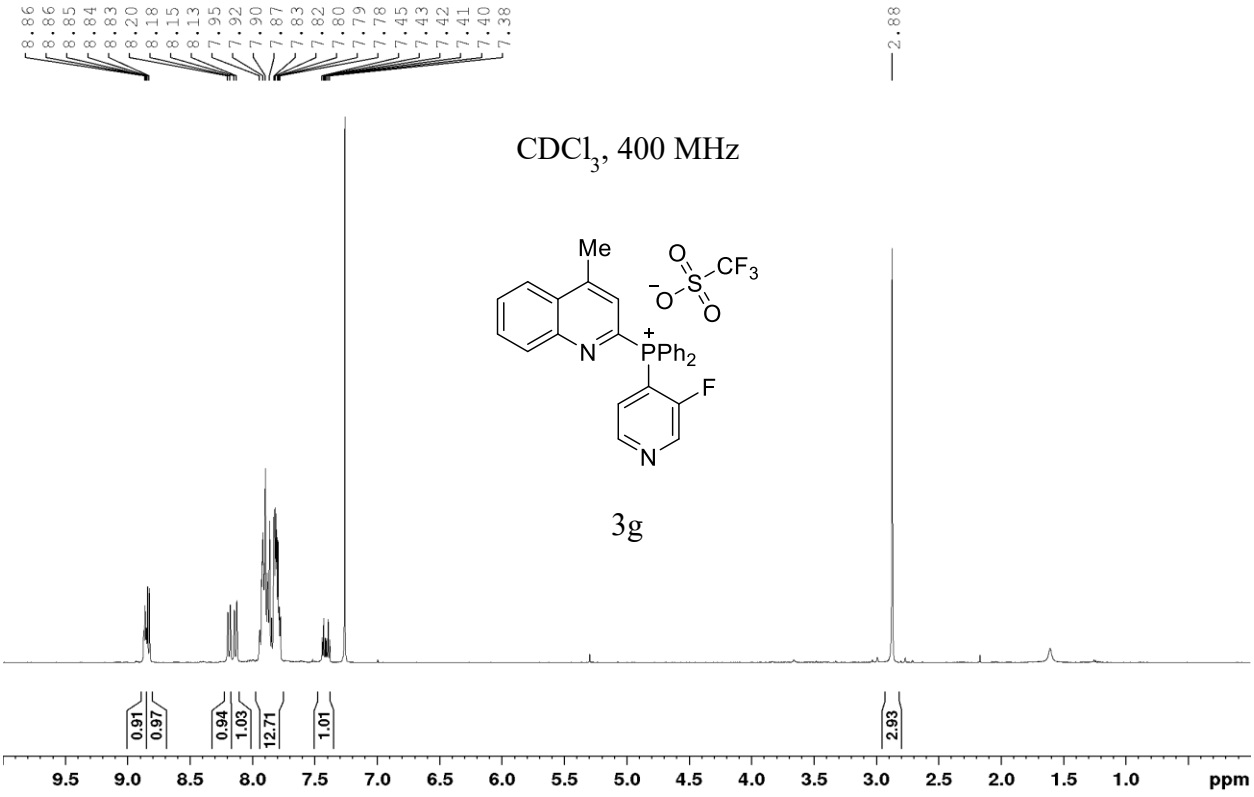


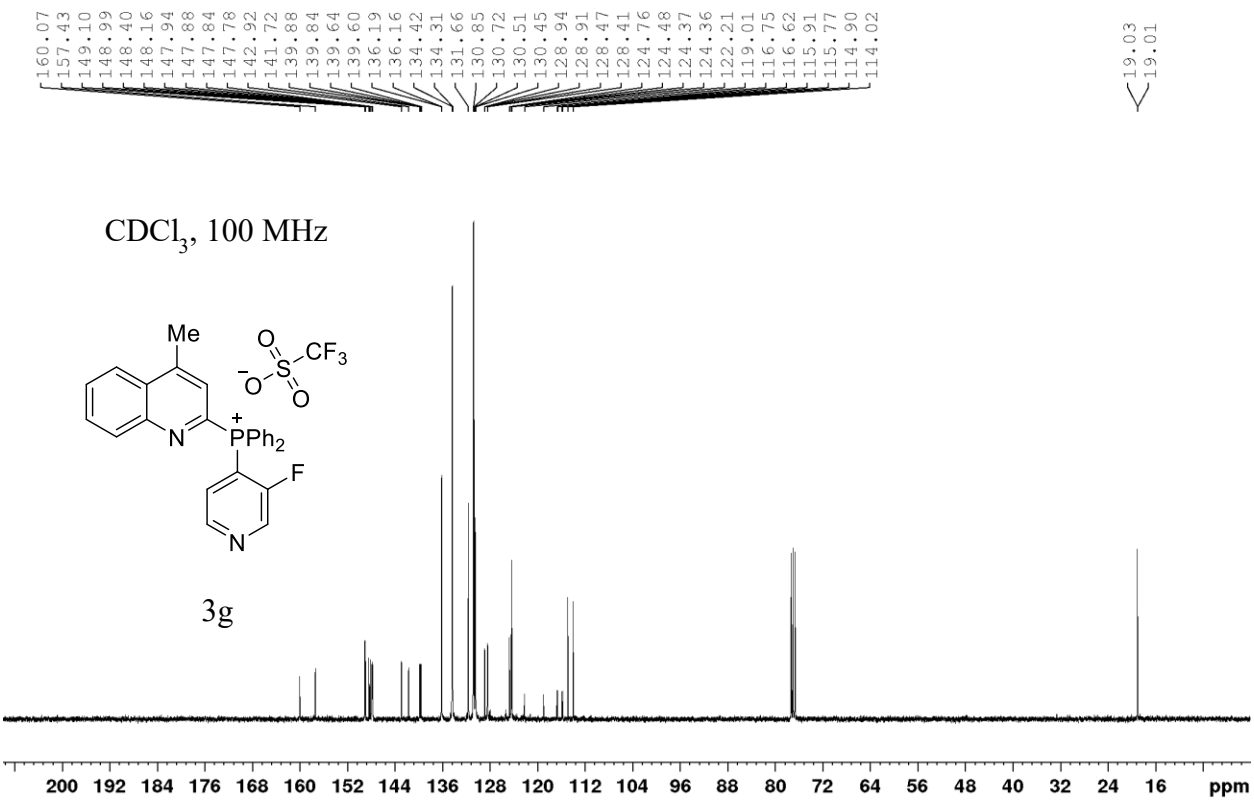
CD_3OD, 100 MHz

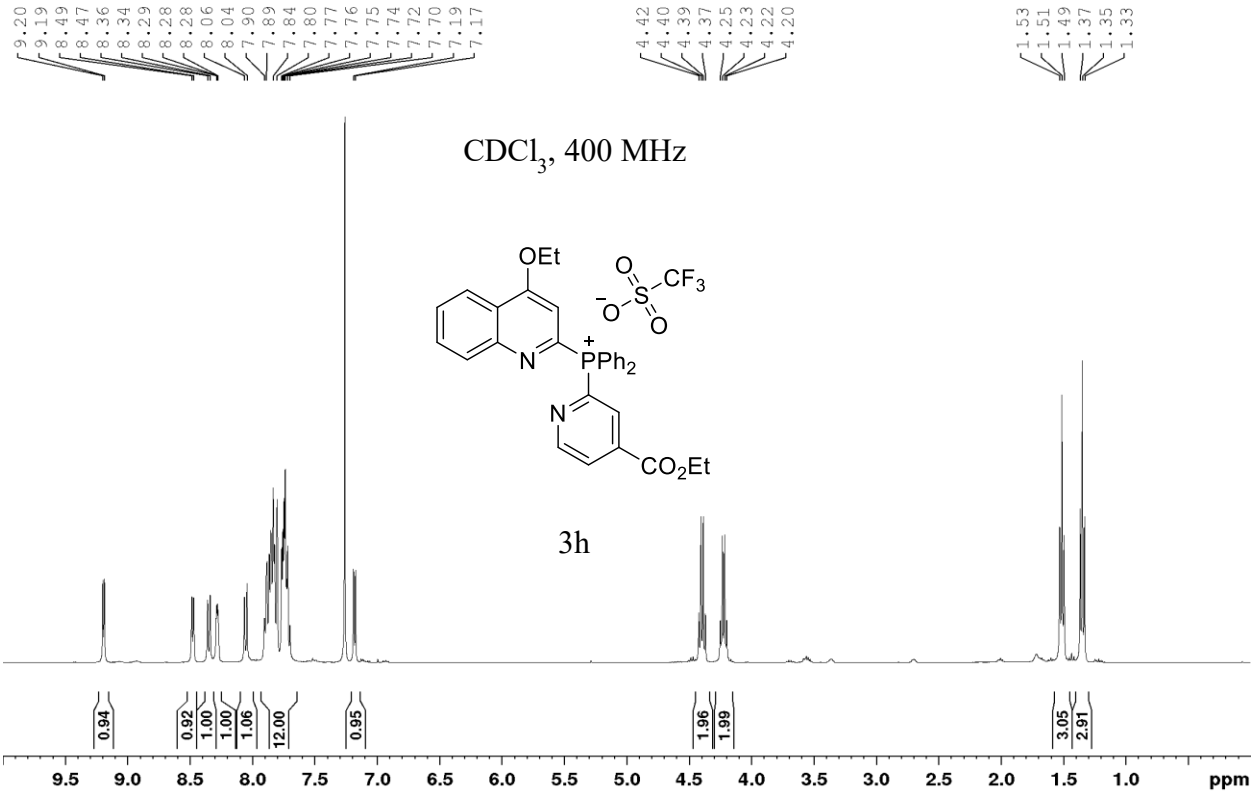


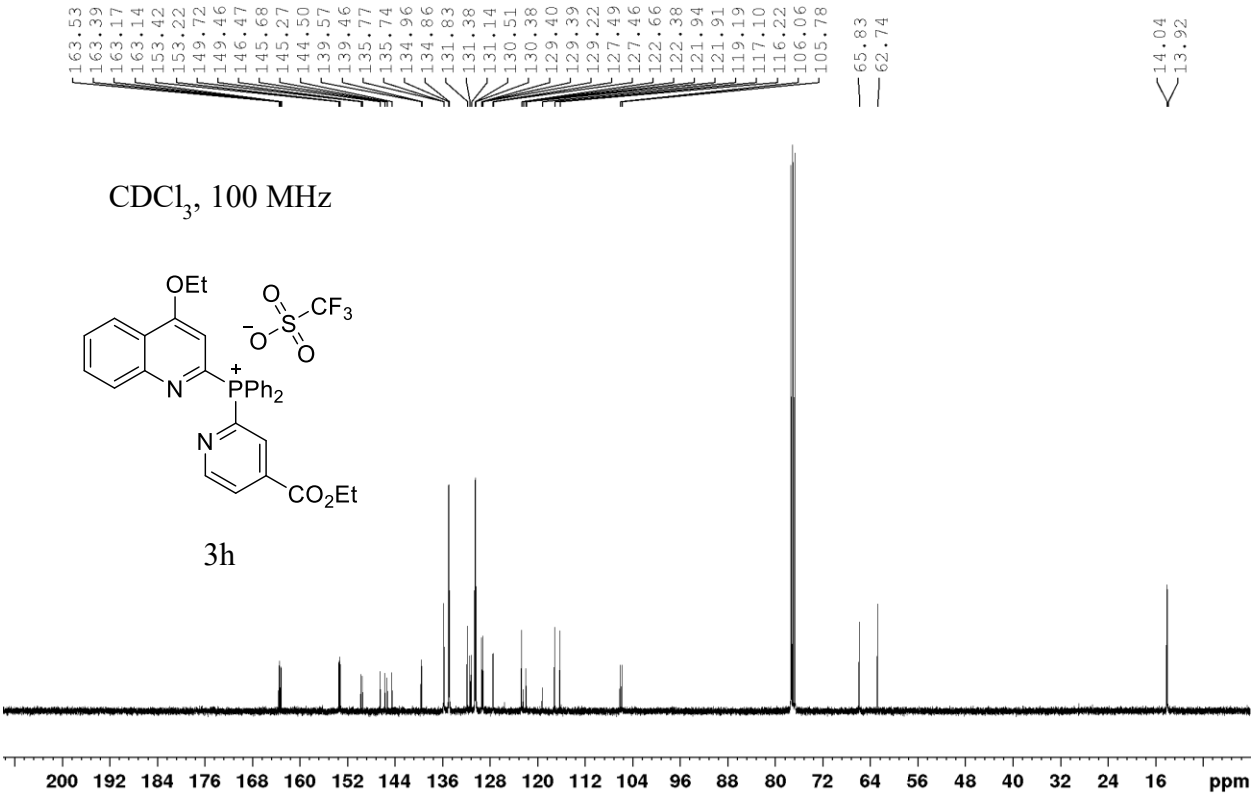

CDCl3, 400 MHz
3f

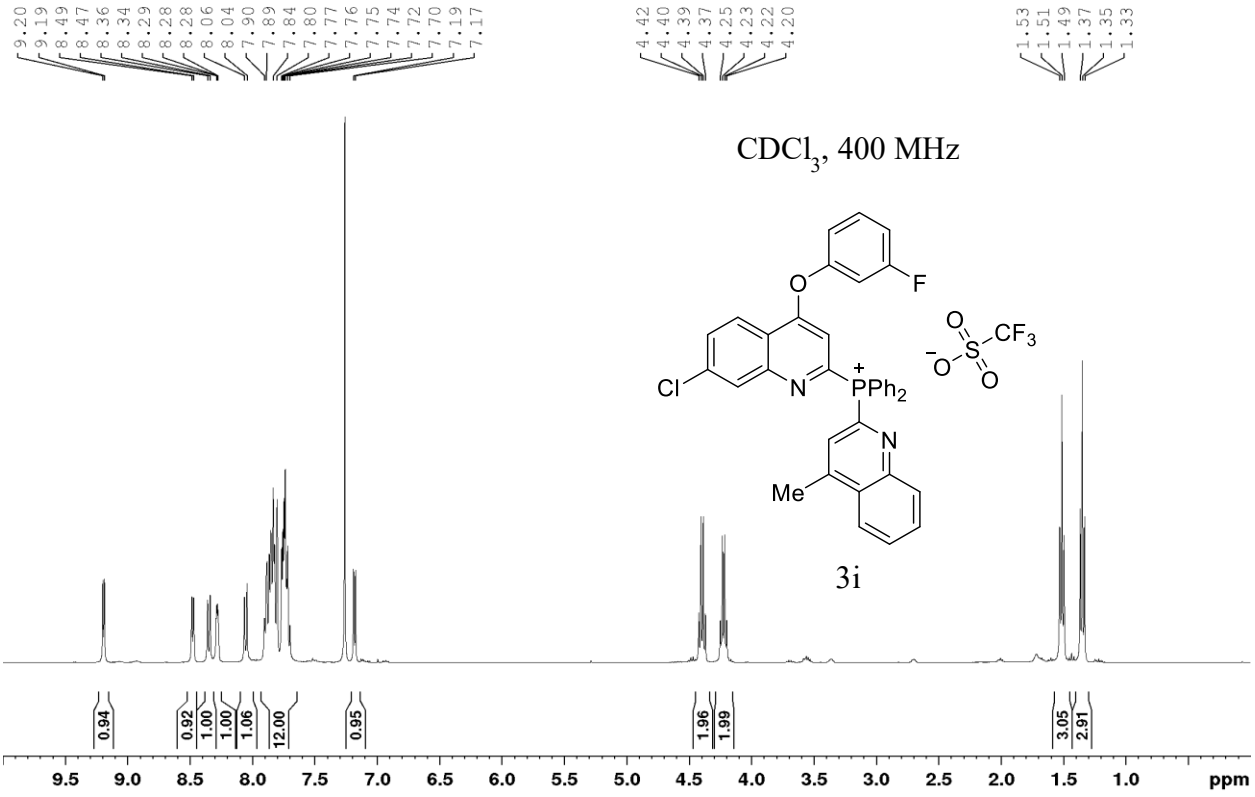

CDCl3, 100 MHz
3f

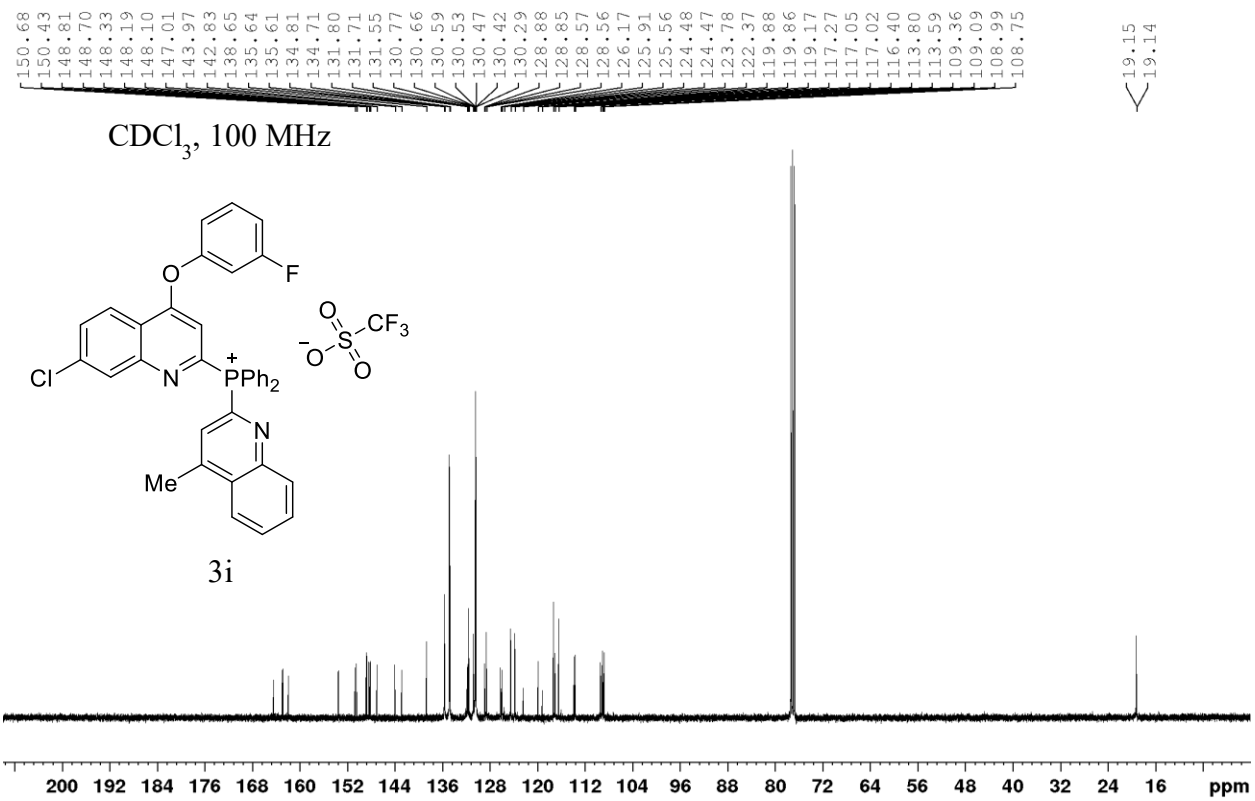

8.86
8.86
8.85
8.84
8.83
8.20
8.18
8.15
8.13
7.95
7.92
7.90
7.87
7.83
7.82
7.80
7.79
7.78
7.45
7.43
7.42
7.41
7.40
7.38
2.88
CDCl3, 400 MHz
Me
O
S
CF3
O
O
N
PPh2
F
N
3g
0.91
0.97
0.94
1.03
12.71
1.01
2.93
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

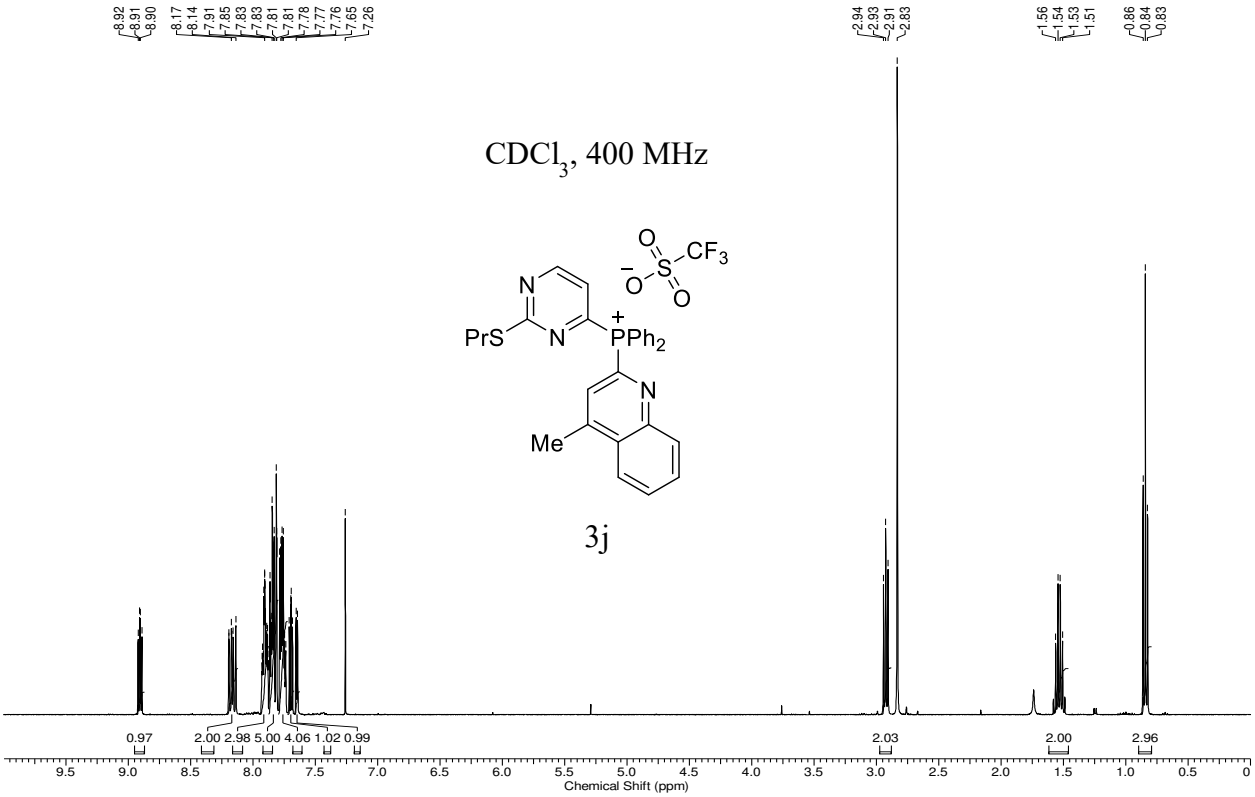

160.07
157.43
149.10
148.99
148.40
148.16
147.94
147.88
147.84
147.78
142.92
141.72
139.88
139.84
139.64
139.60
136.19
136.16
134.42
134.31
131.66
130.85
130.72
130.51
130.45
128.94
128.91
128.47
128.41
124.76
124.48
124.37
124.36
122.21
119.01
116.75
116.62
115.91
115.77
114.90
114.02
19.03
19.01
CDCl3, 100 MHz
Me
O
S
CF3
O
O
N
PPh2
F
N
3g
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
ppm

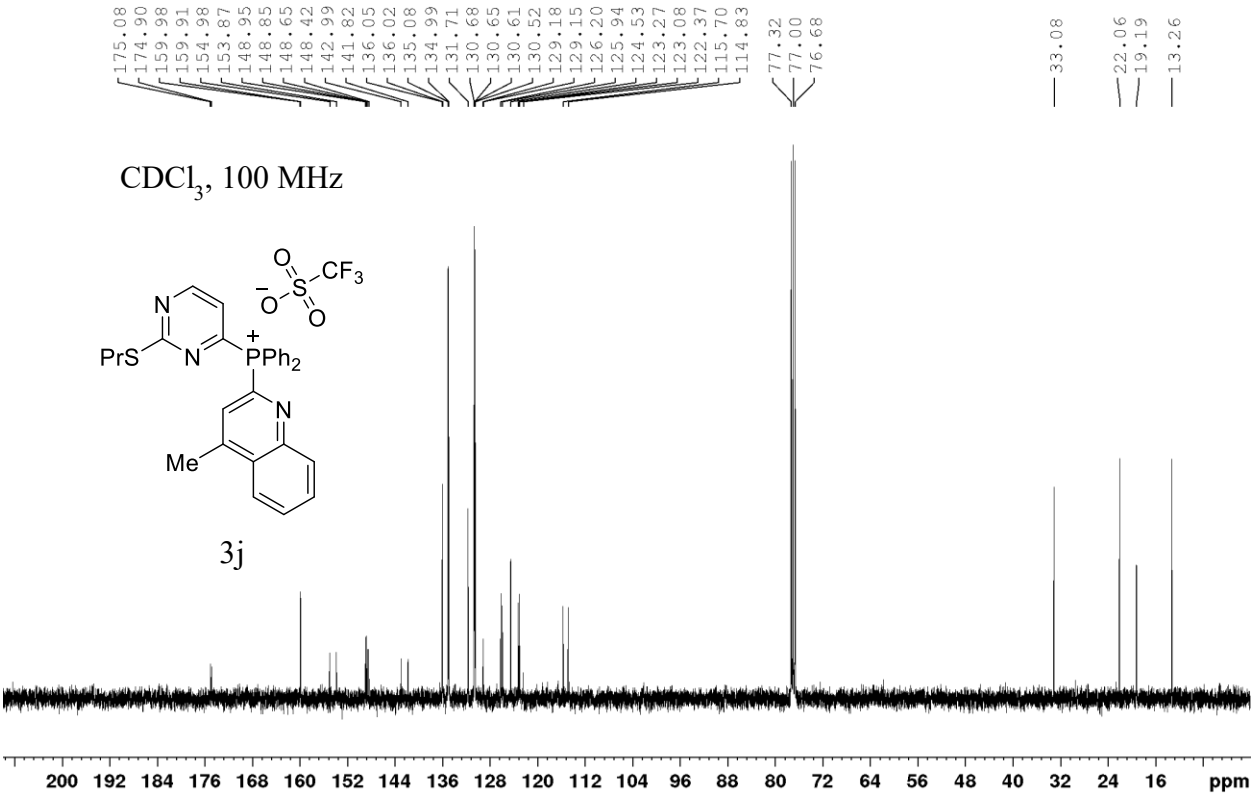

9.20
9.19
8.49
8.47
8.36
8.34
8.29
8.28
8.28
8.06
8.04
7.90
7.89
7.84
7.80
7.77
7.76
7.75
7.74
7.72
7.70
7.19
7.17
4.42
4.40
4.39
4.37
4.25
4.23
4.22
4.20
1.53
1.51
1.49
1.37
1.35
1.33
CDCl3, 400 MHz
OEt
CF3
PPh2
CO2Et
3h
0.94
0.92
1.00
1.00
1.06
12.00
0.95
1.96
1.99
3.05
2.91
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

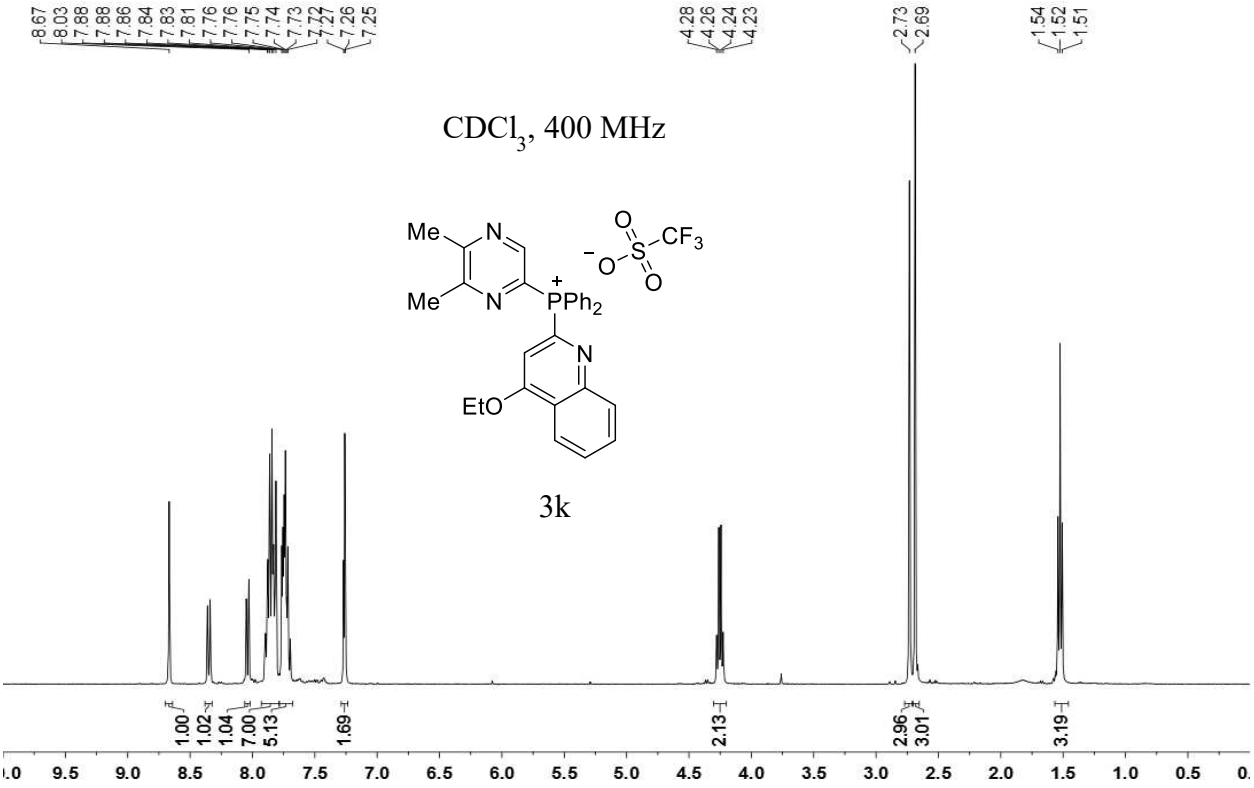

163.53
163.39
163.17
163.14
153.42
153.22
149.72
149.46
146.47
145.68
145.27
144.50
139.57
139.46
135.77
135.74
134.96
134.86
131.83
131.38
131.14
130.51
130.38
129.40
129.39
129.22
127.49
127.46
122.66
122.38
121.94
121.91
119.19
117.10
116.22
106.06
105.78
65.83
62.74
14.04
13.92
CDCl3, 100 MHz
OEt
CF3
PPh2
CO2Et
3h
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16
ppm

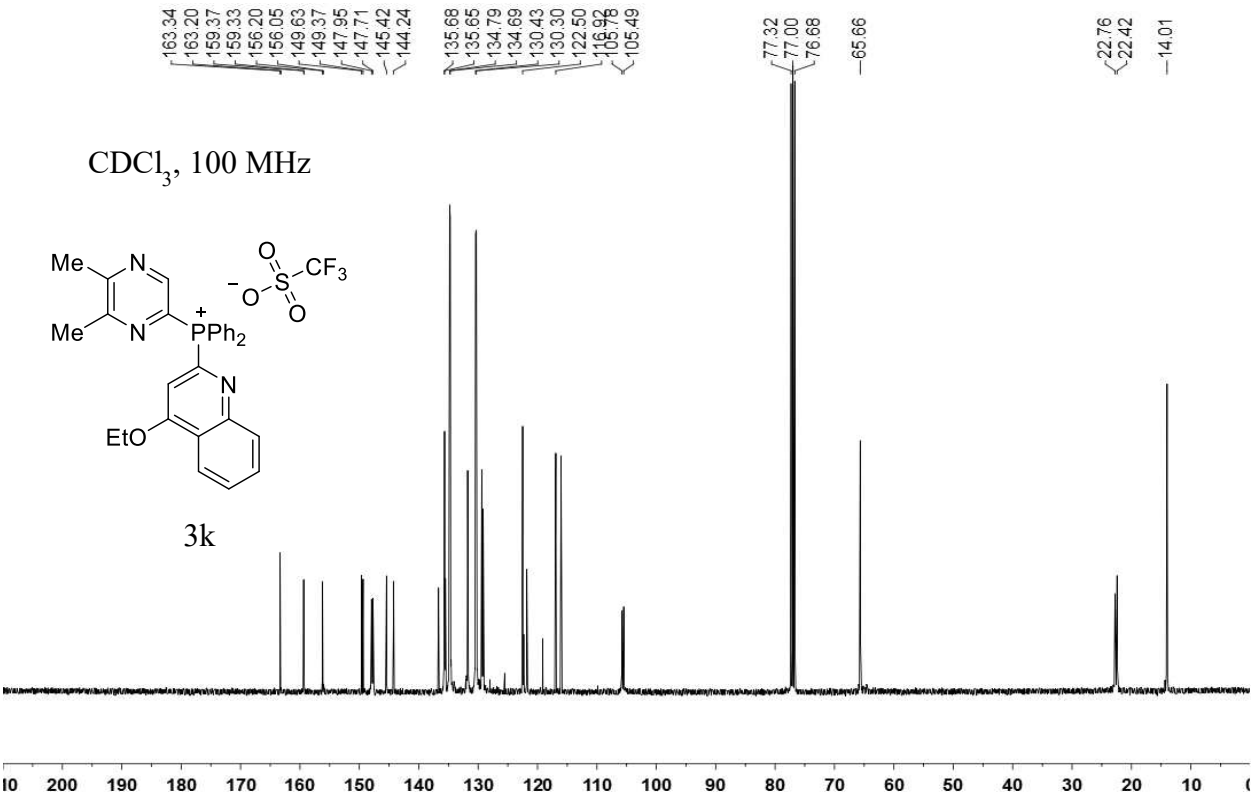

9.20
9.19
8.49
8.47
8.36
8.34
8.29
8.28
8.28
8.06
8.04
7.90
7.89
7.84
7.80
7.77
7.76
7.75
7.74
7.72
7.70
7.19
7.17
4.42
4.40
4.39
4.37
4.25
4.23
4.22
4.20
1.53
1.51
1.49
1.37
1.35
1.33
CDCl3, 400 MHz
O
F
Cl
N
PPh2
O
S
CF3
O
O
N
Me
3i
0.94
0.92
1.00
1.00
1.06
12.00
0.95
1.96
1.99
3.05
2.91
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

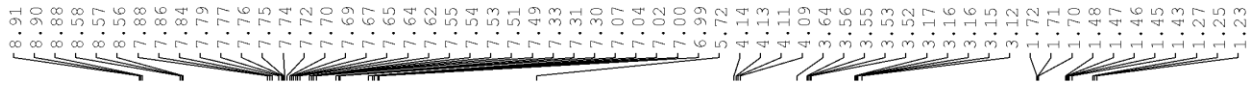

150.68
150.43
148.81
148.70
148.33
148.19
148.10
147.01
143.97
142.83
138.65
135.64
135.61
134.81
134.71
131.80
131.71
131.55
130.77
130.66
130.59
130.53
130.47
130.42
130.29
128.88
128.85
128.57
128.56
126.17
125.91
125.56
124.48
124.47
123.78
122.37
119.88
119.86
119.17
117.27
117.05
117.02
116.40
113.80
113.59
109.36
109.09
108.99
108.75
19.15
19.14
CDCl3, 100 MHz
O
F
Cl
N
PPh2
O
S
CF3
O
O
N
Me
3i
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
ppm


8.92
8.91
8.90
8.17
8.14
7.91
7.85
7.83
7.83
7.83
7.81
7.81
7.78
7.77
7.76
7.65
7.26
2.94
2.93
2.91
2.83
1.56
1.54
1.53
1.51
0.86
0.84
0.83
CDCl3, 400 MHz
PrS
PPh2
Me
3j
0.97
2.00
2.98
5.00
4.06
1.02
0.99
2.03
2.00
2.96
Chemical Shift (ppm)

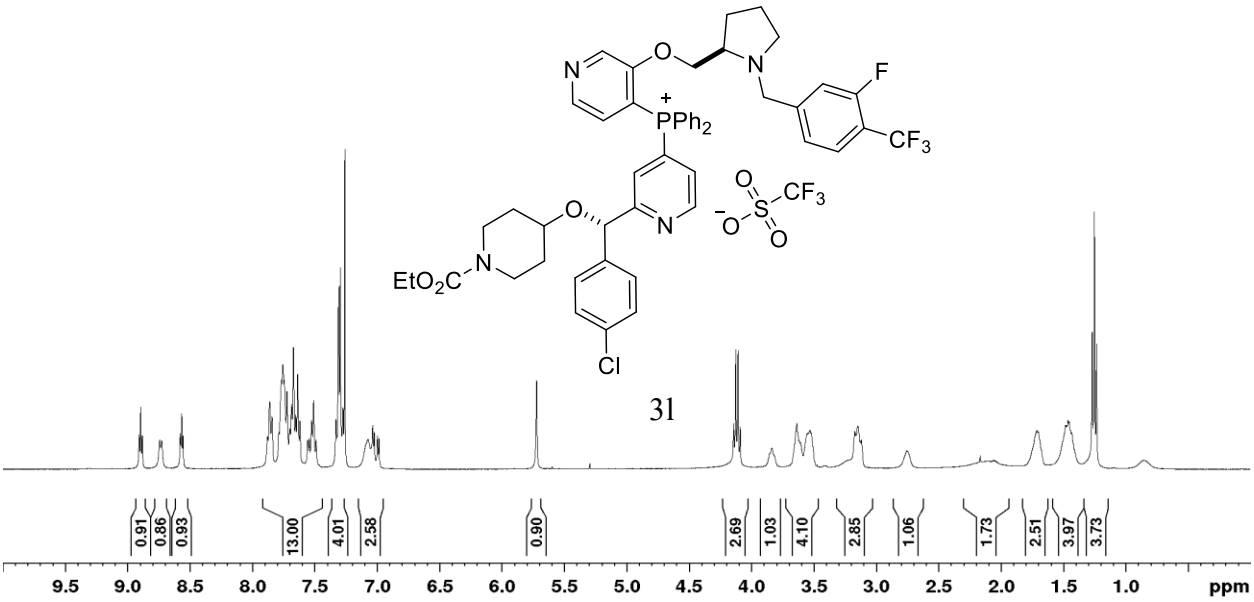

175.08
174.90
159.98
159.91
154.98
153.87
148.95
148.85
148.65
148.42
142.99
141.82
136.05
136.02
135.08
134.99
131.71
130.68
130.65
130.61
130.52
129.18
129.15
126.20
125.94
124.53
123.27
123.08
122.37
115.70
114.83
77.32
77.00
76.68
33.08
22.06
19.19
13.26
CDCl3, 100 MHz
PrS
PPh2
Me
3j
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
ppm


8.67
8.03
7.88
7.88
7.86
7.84
7.83
7.81
7.76
7.76
7.75
7.74
7.73
7.72
7.27
7.26
7.25
4.28
4.26
4.24
4.23
2.73
2.69
1.54
1.52
1.51
CDCl3, 400 MHz
Me
N
Me
N
PPh2
O
S
CF3
O
O
O
N
EtO
3k
1.00
1.02
1.04
7.00
5.13
1.69
2.13
2.96
3.01
3.19
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

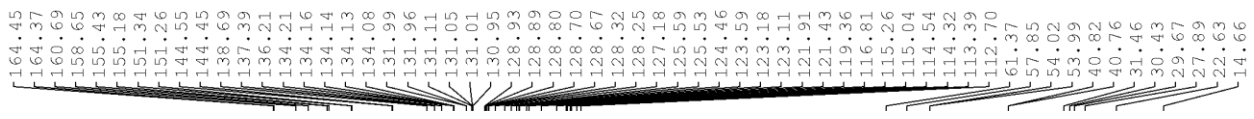

163.34
163.20
159.37
159.33
156.20
156.05
149.63
149.37
147.95
147.71
145.42
144.24
135.68
135.65
134.79
134.69
130.43
130.30
122.50
77.32
77.00
76.68
65.66
22.76
22.42
14.01
CDCl3, 100 MHz
Me
N
Me
N
PPh2
O
S
CF3
O
O
O
N
EtO
3k
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



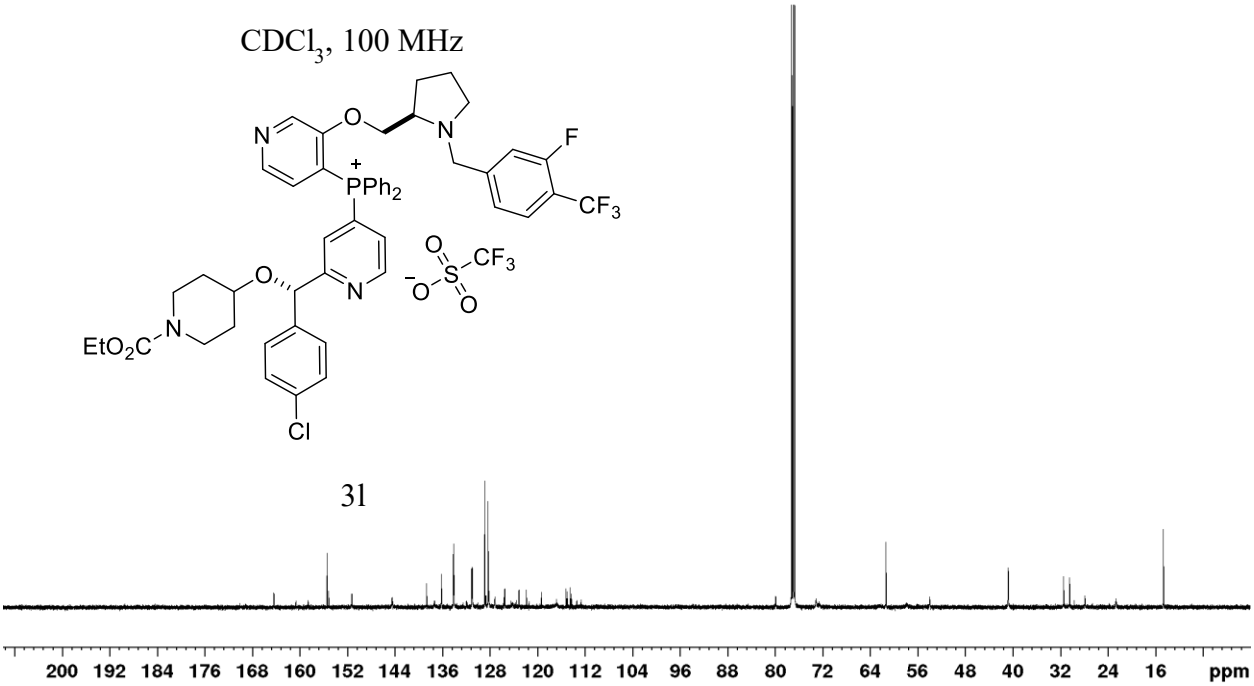
$CDCl_3$, 400 MHz



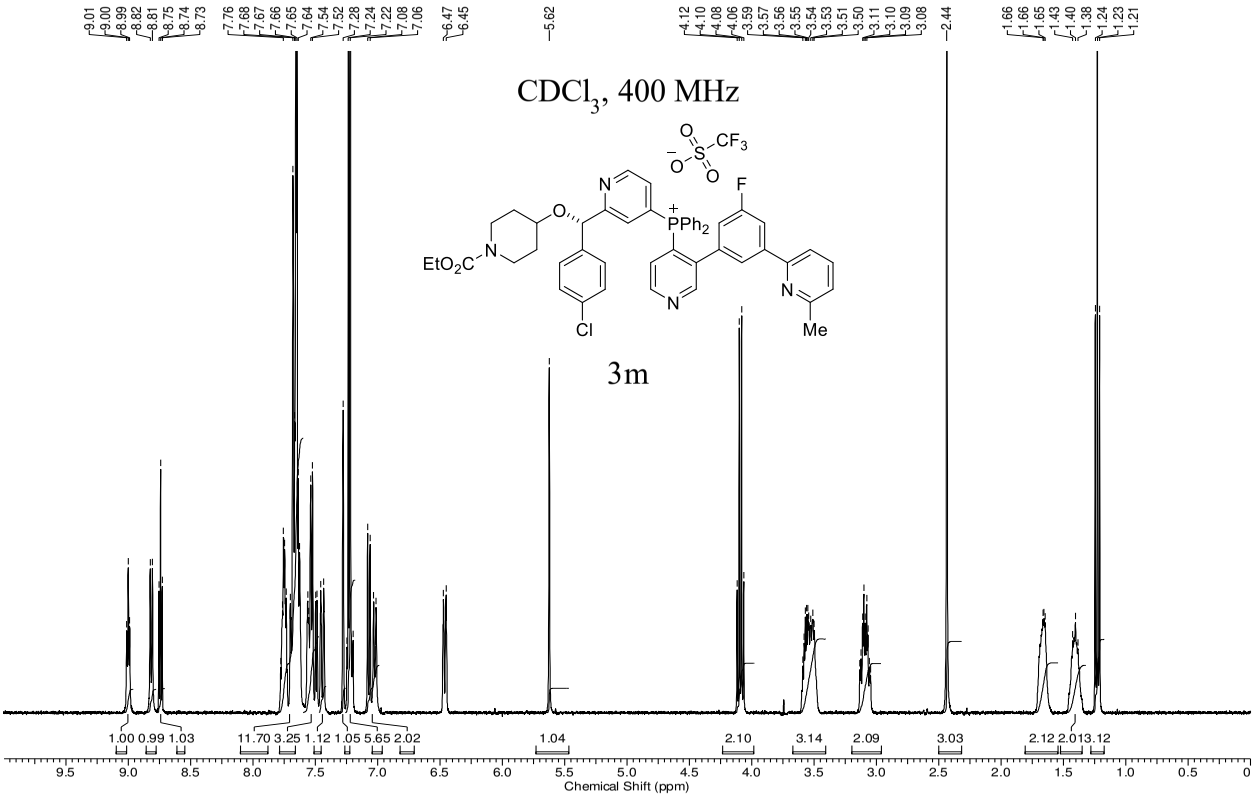
31

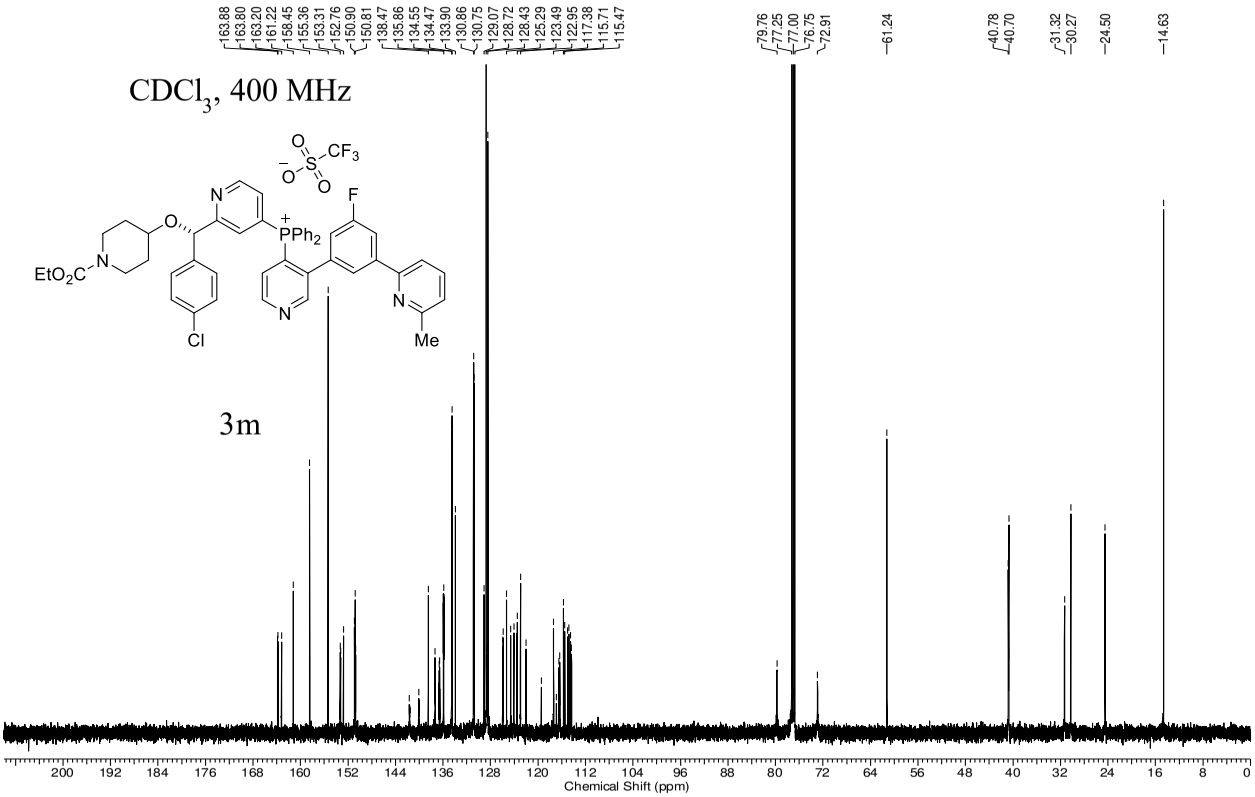


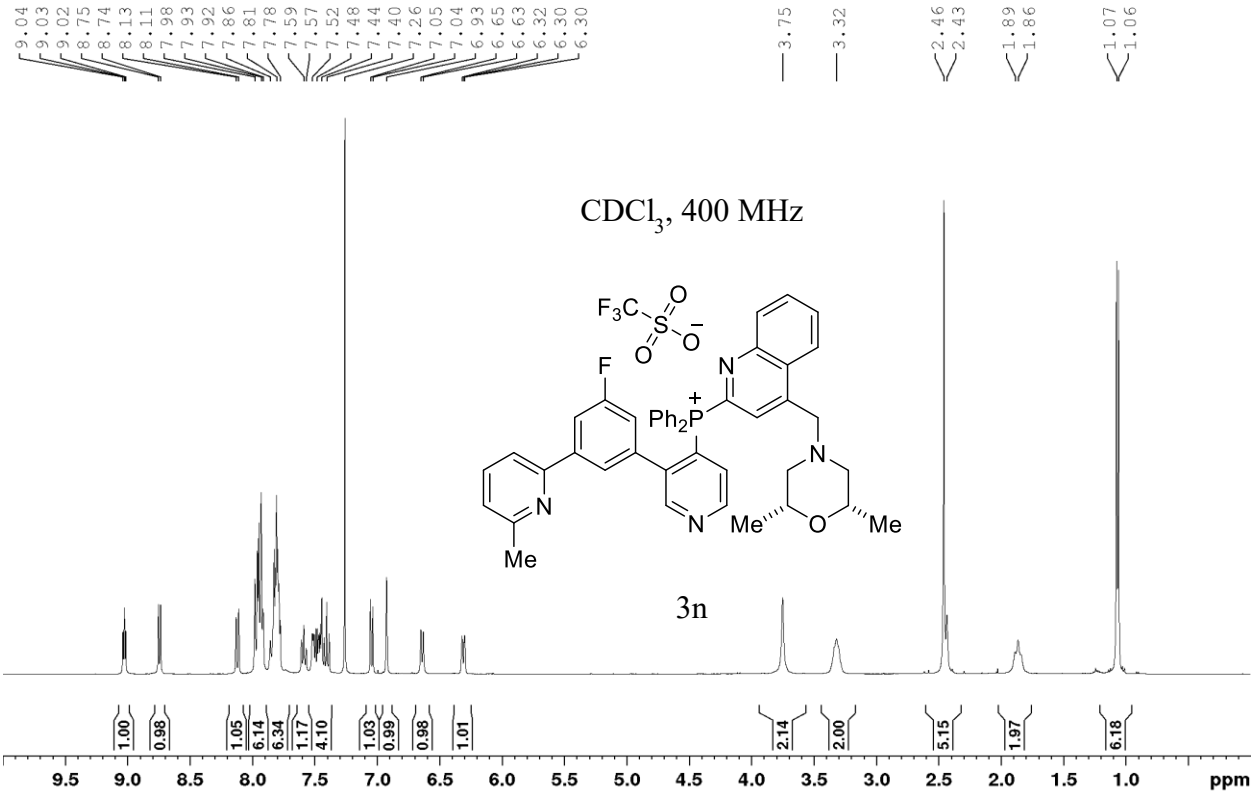
$CDCl_3$, 100 MHz

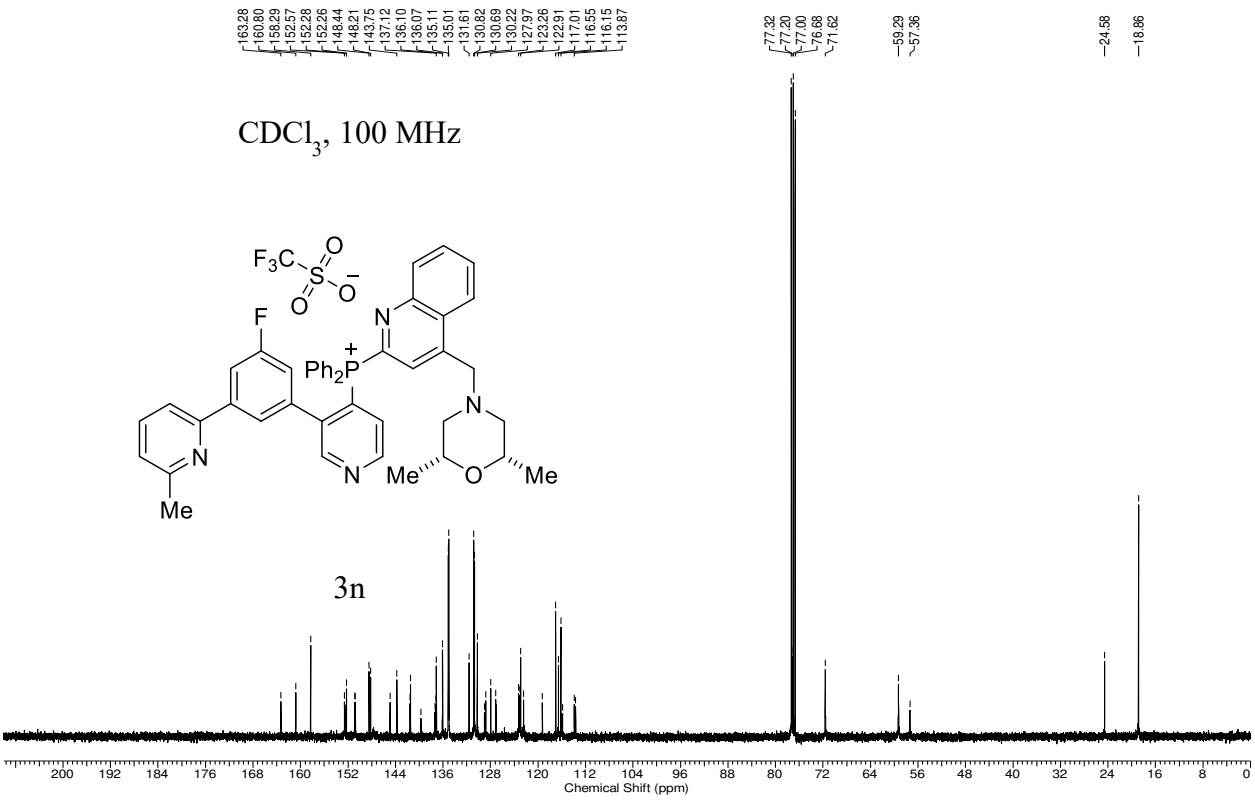


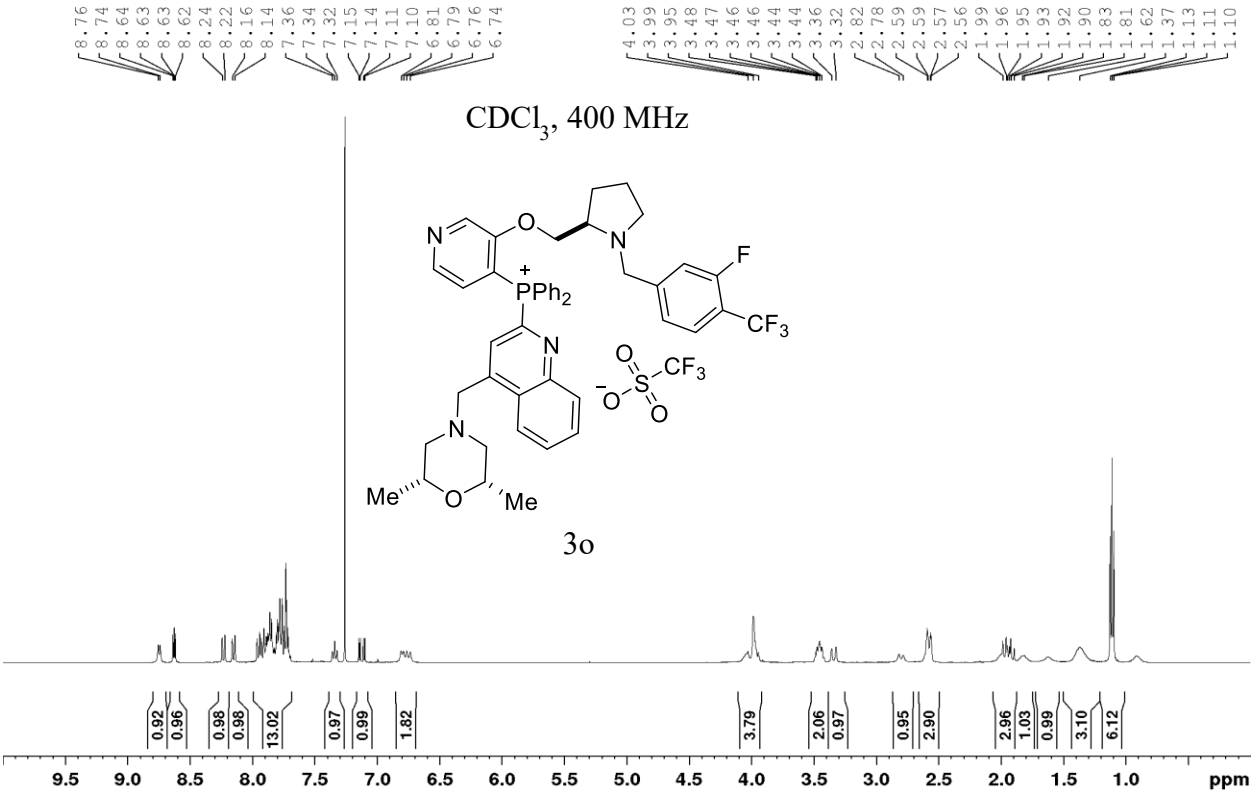
31

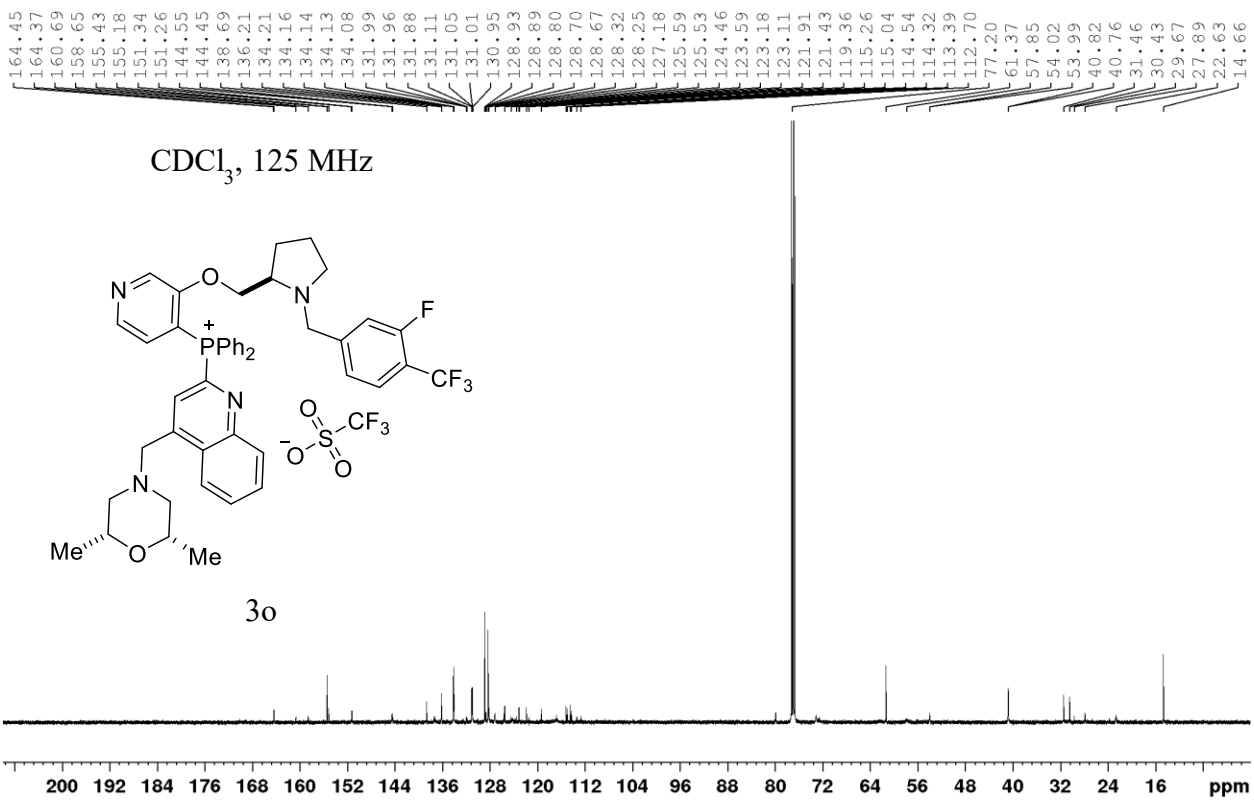

CDCl3, 400 MHz
3m
Chemical Shift (ppm)

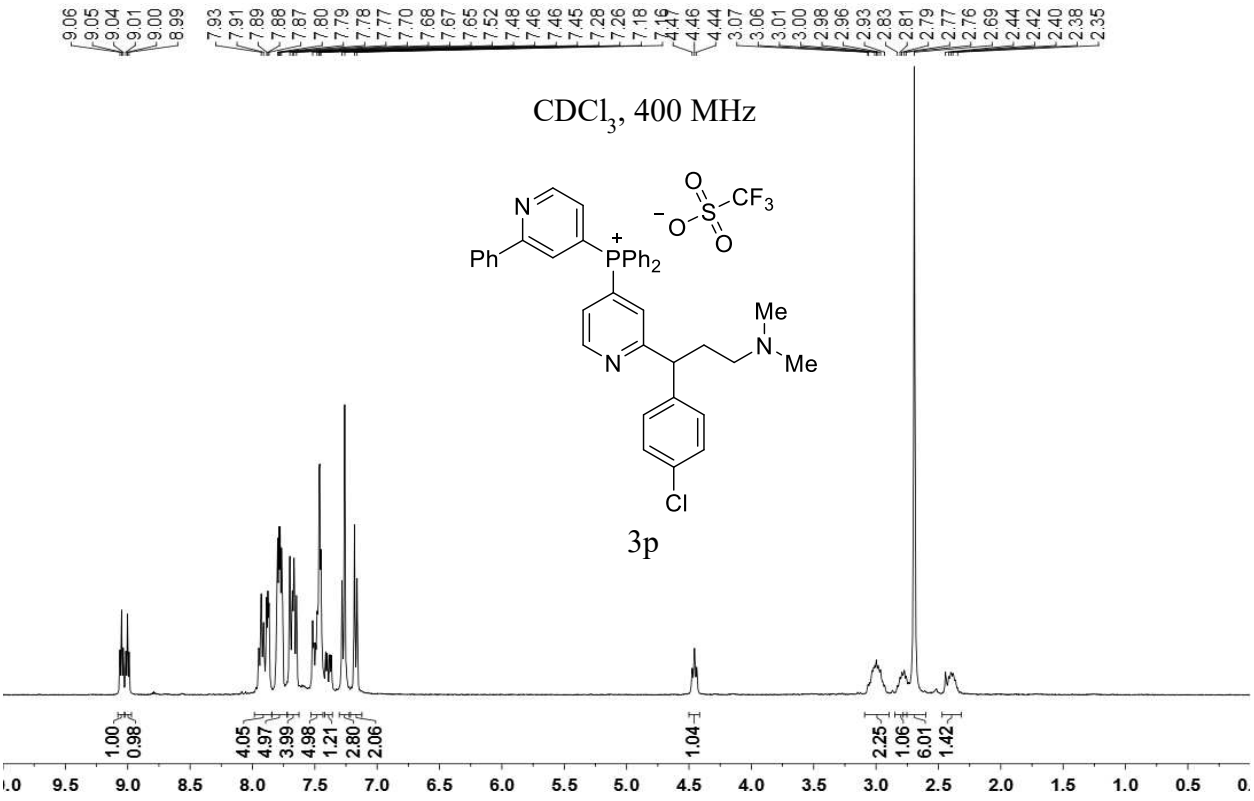

CDCl3, 400 MHz
3m
Chemical Shift (ppm)

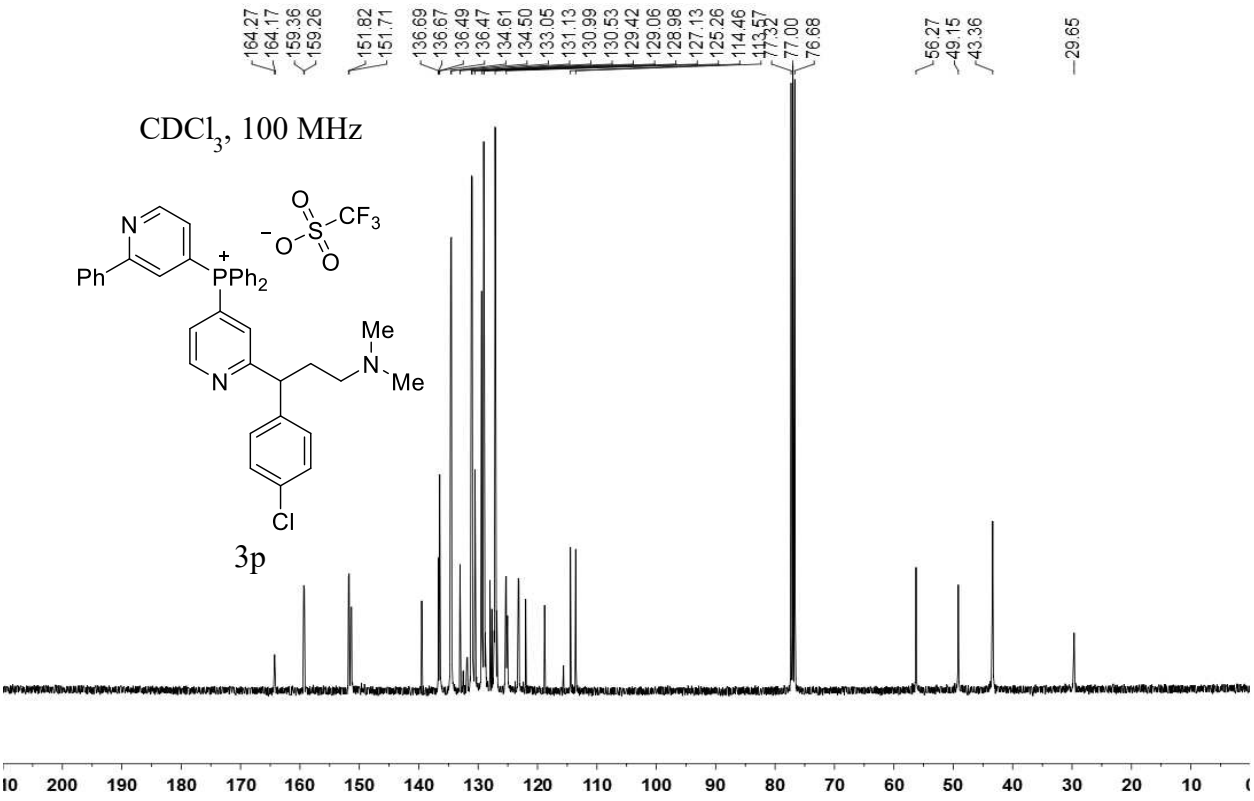

CDCl3, 400 MHz
3n
ppm

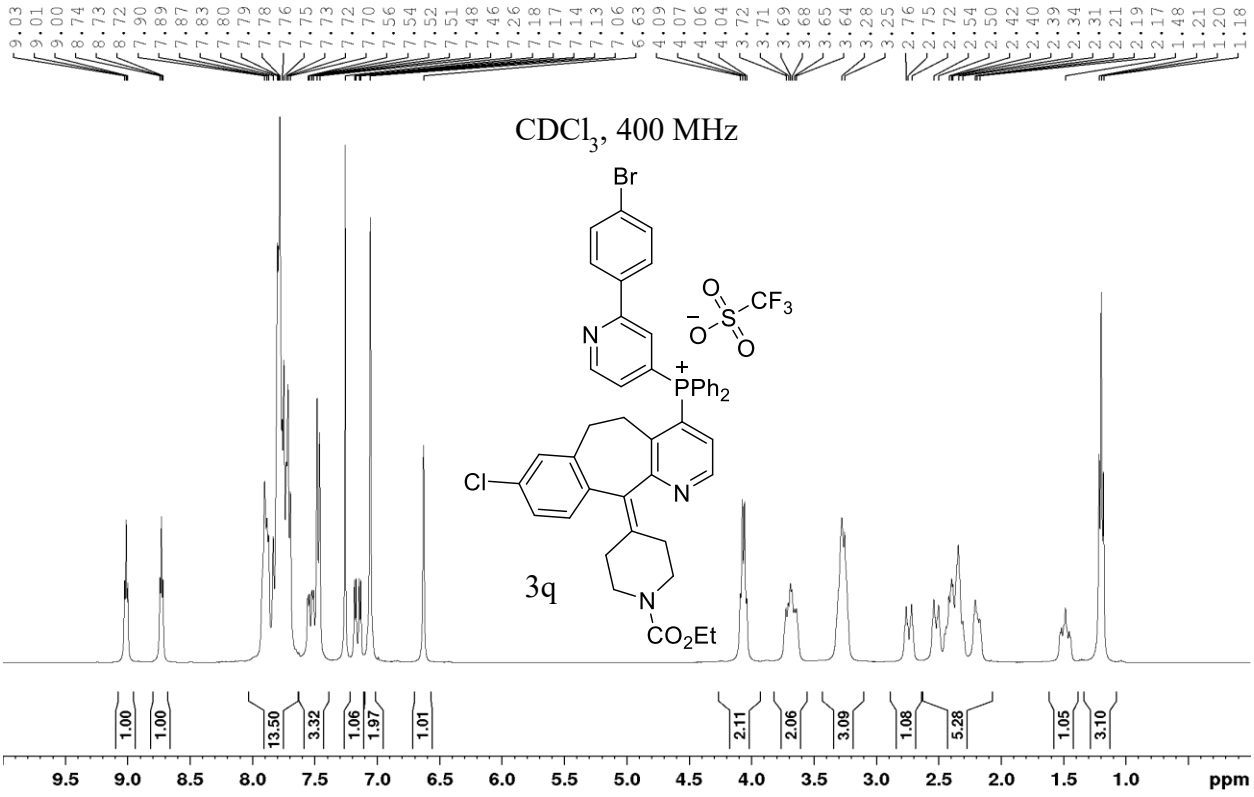

CDCl3, 100 MHz
3n
Chemical Shift (ppm)

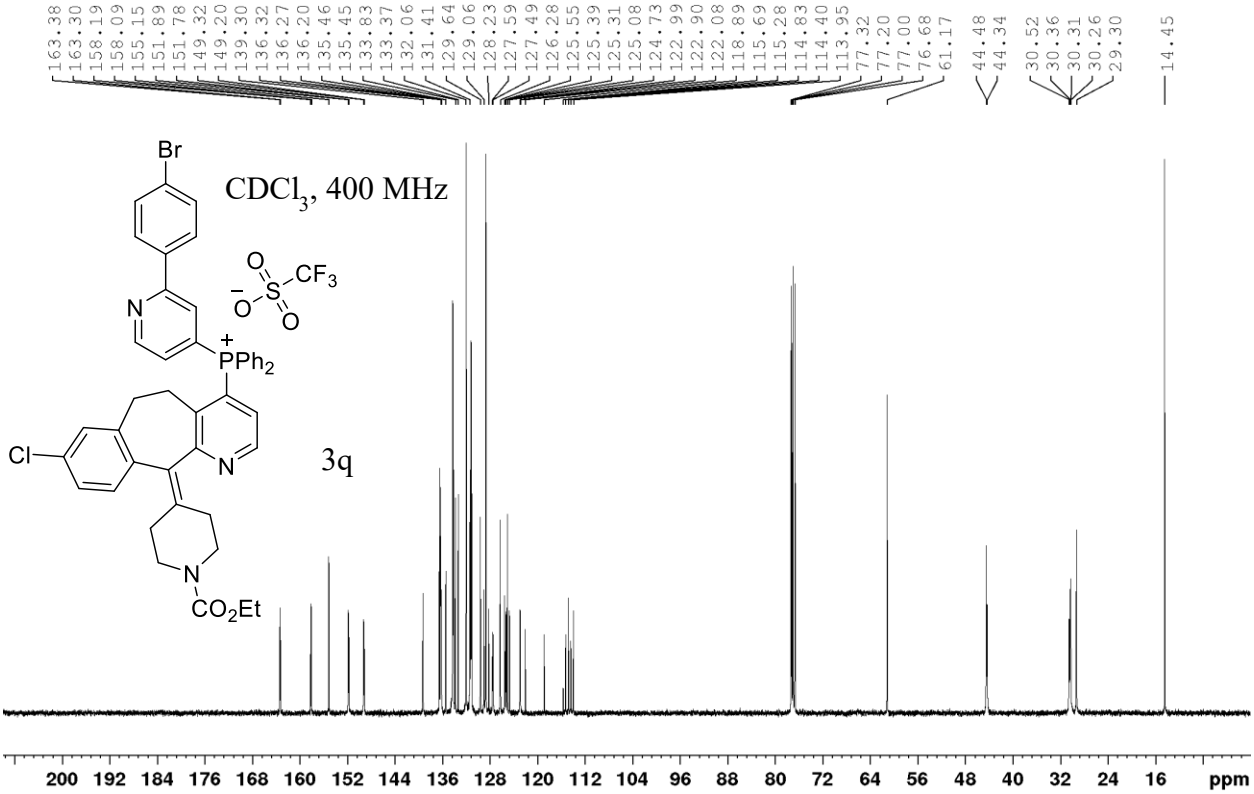

8.76
8.74
8.64
8.63
8.63
8.62
8.24
8.22
8.16
8.14
7.36
7.34
7.32
7.15
7.14
7.11
7.10
6.81
6.79
6.76
6.74
4.03
3.99
3.95
3.48
3.47
3.46
3.46
3.44
3.36
3.32
2.82
2.78
2.59
2.59
2.57
2.56
1.99
1.96
1.95
1.93
1.92
1.90
1.83
1.81
1.62
1.37
1.13
1.11
1.10
CDCl3, 400 MHz
3o
0.92
0.96
0.98
0.98
13.02
0.97
0.99
1.82
3.79
2.06
0.97
0.95
2.90
2.96
1.03
0.99
3.10
6.12
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

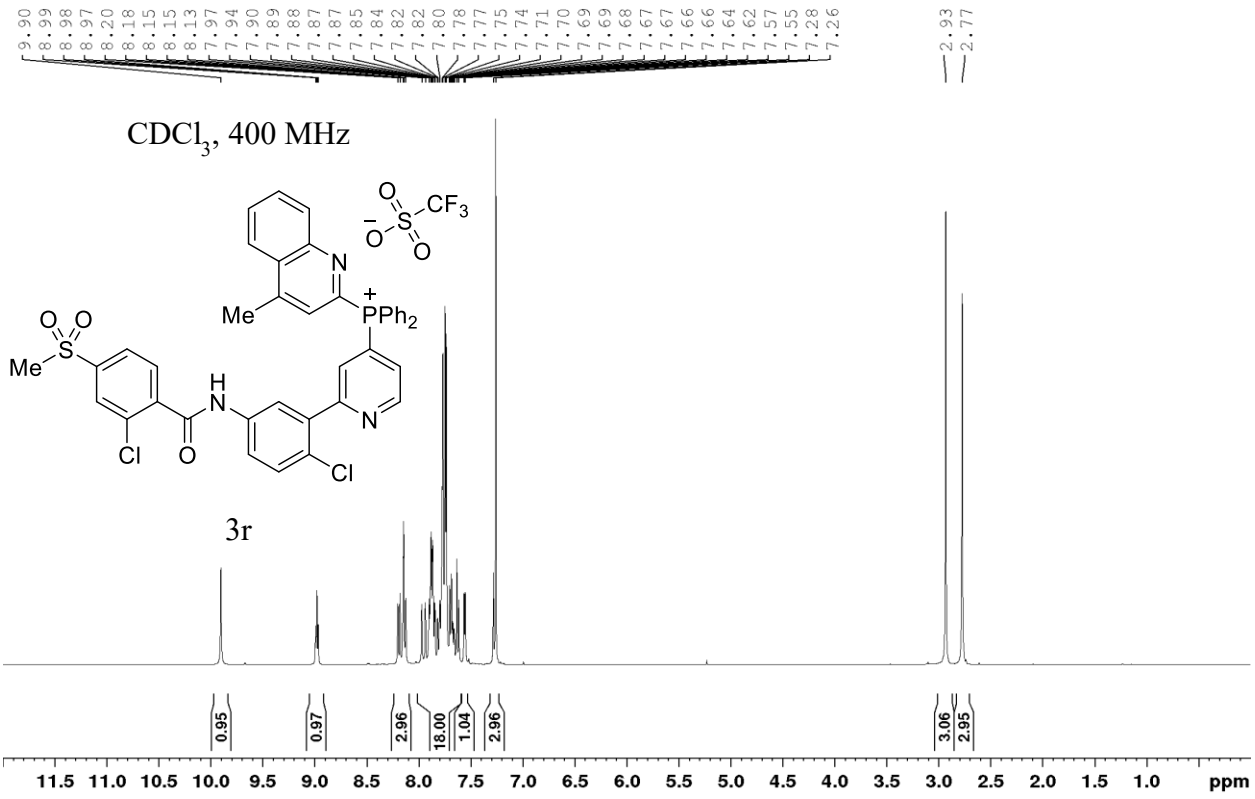

164.45
164.37
160.69
158.65
155.43
155.18
151.34
151.26
144.55
144.45
138.69
136.21
134.21
134.16
134.14
134.13
134.08
131.99
131.96
131.88
131.11
131.05
131.01
130.95
128.93
128.89
128.80
128.70
128.67
128.32
128.25
127.18
125.59
125.53
124.46
123.59
123.18
123.11
121.91
121.43
119.36
115.26
115.04
114.54
114.32
113.39
112.70
77.20
61.37
57.85
54.02
53.99
40.82
40.76
31.46
30.43
29.67
27.89
22.63
14.66
CDCl3, 125 MHz
3o
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16
ppm

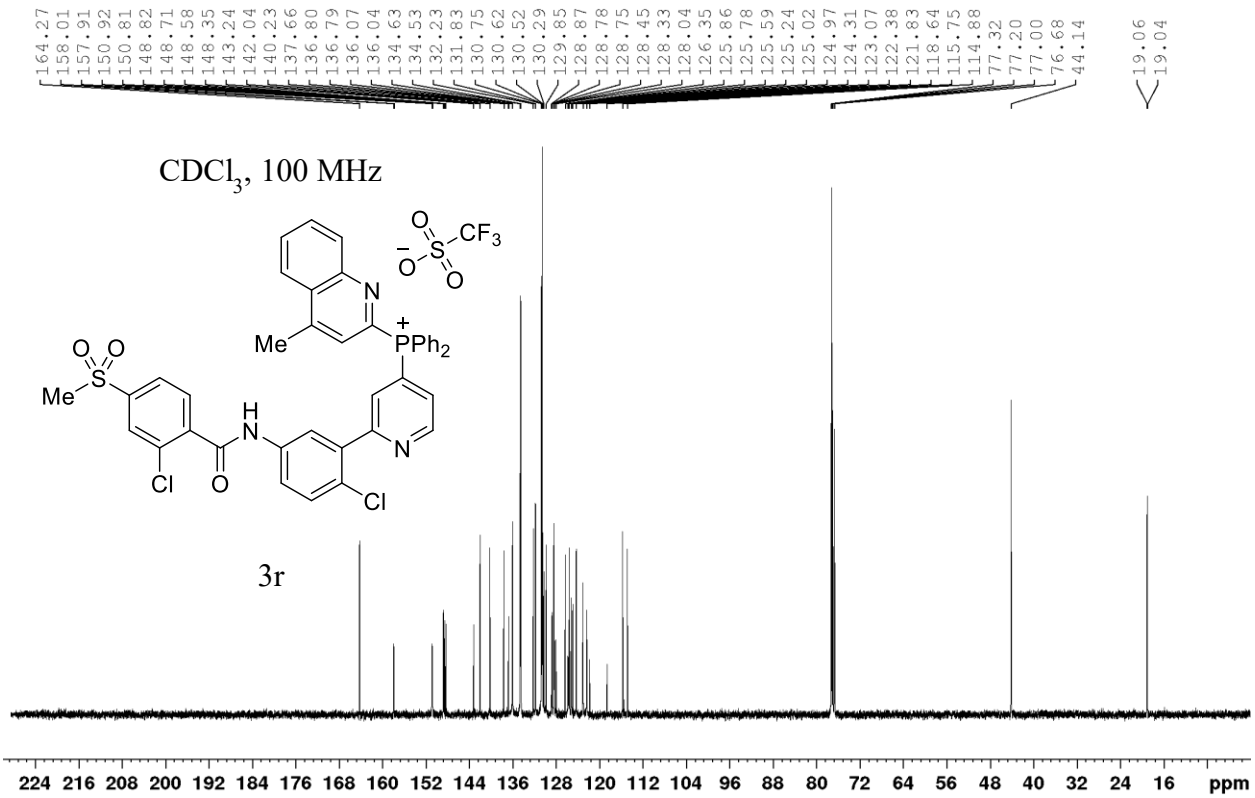

CDCl3, 400 MHz
3p

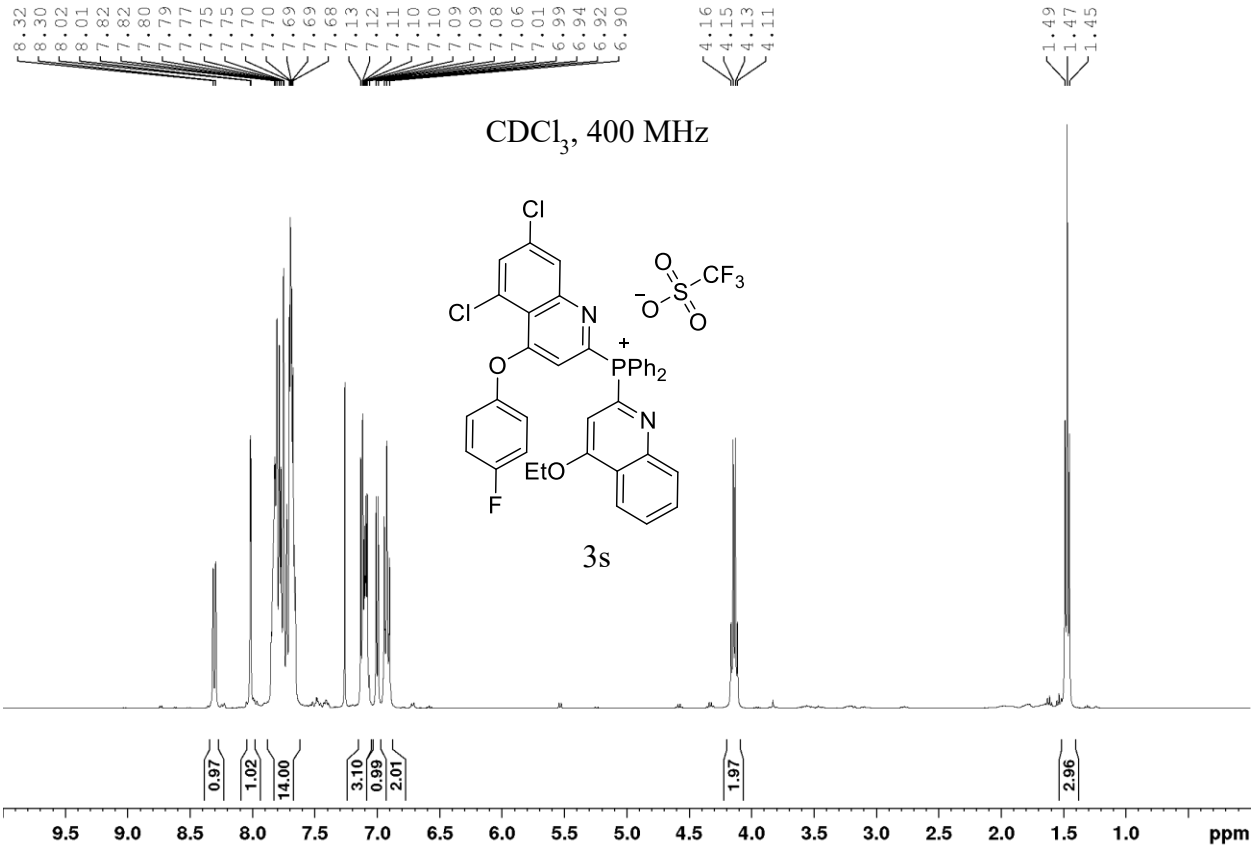

CDCl3, 100 MHz
3p

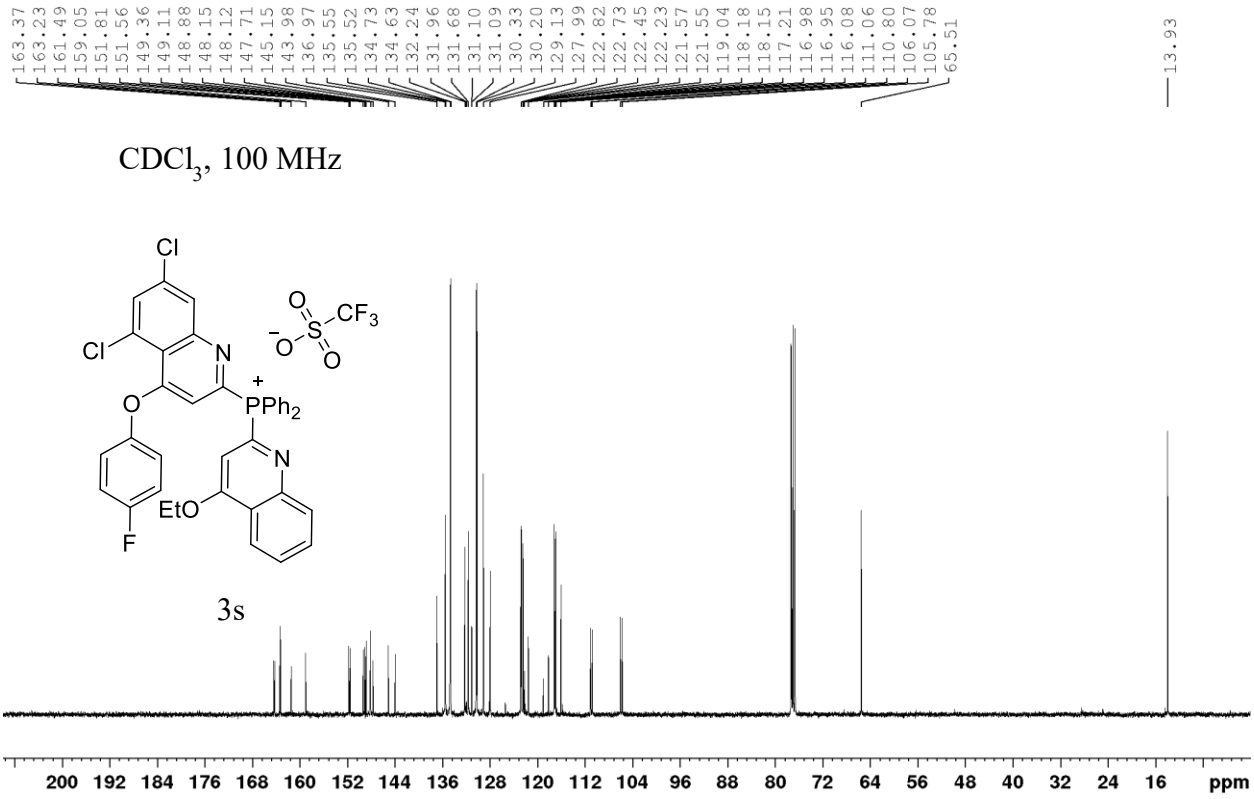

9.03 9.01 9.00 8.74 8.73 8.72 7.90 7.89 7.87 7.83 7.80 7.79 7.78 7.76 7.75 7.73 7.72 7.70 7.56 7.54 7.52 7.51 7.48 7.46 7.26 7.18 7.17 7.14 7.13 7.06 6.63 4.09 4.07 4.06 4.04 3.72 3.71 3.69 3.68 3.65 3.64 3.28 3.25 2.76 2.75 2.72 2.54 2.50 2.42 2.40 2.39 2.34 2.31 2.21 2.19 2.17 1.48 1.21 1.20 1.18
CDCl3, 400 MHz
3q
1.00 1.00 13.50 3.32 1.06 1.97 1.01 2.11 2.06 3.09 1.08 5.28 1.05 3.10
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

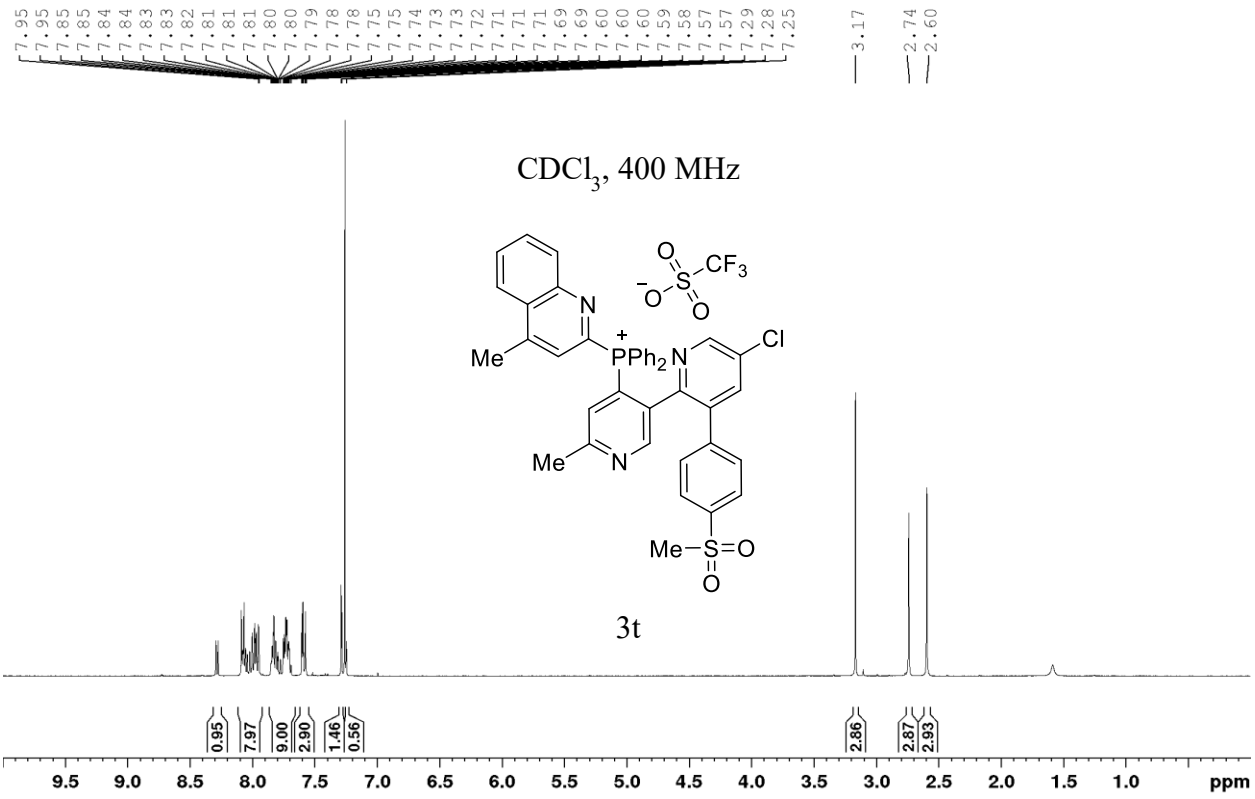

163.38 163.30 158.19 158.09 155.15 151.89 151.78 149.32 149.20 139.30 136.32 136.27 136.20 135.46 135.45 133.83 133.37 132.06 131.41 129.64 129.06 128.23 127.59 127.49 126.28 125.55 125.39 125.31 125.08 124.73 122.99 122.90 122.08 118.89 115.69 115.28 114.83 114.40 113.95 77.32 77.20 77.00 76.68 61.17 44.48 44.34 30.52 30.36 30.31 30.26 29.30 14.45
CDCl3, 400 MHz
3q
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

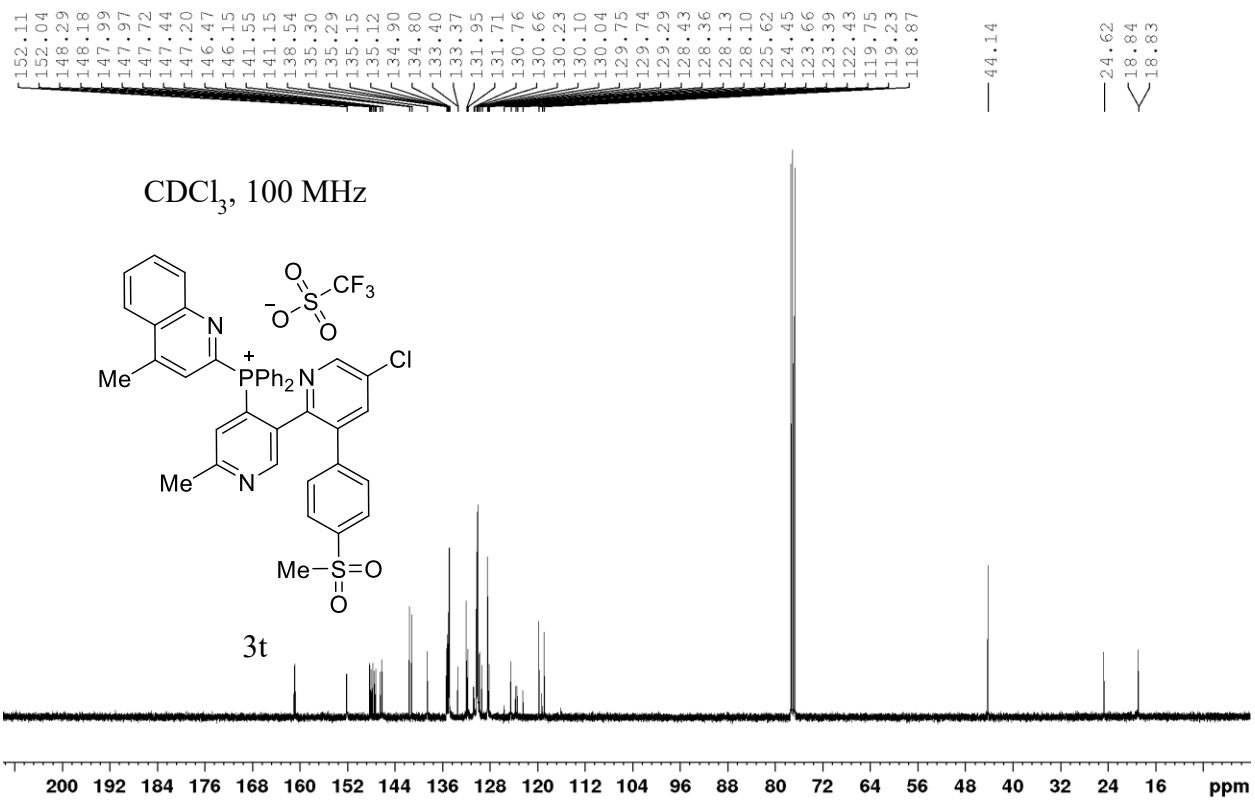

9.90
8.99
8.98
8.97
8.20
8.18
8.15
8.15
8.13
7.97
7.94
7.90
7.89
7.88
7.87
7.87
7.85
7.84
7.82
7.82
7.80
7.78
7.77
7.75
7.74
7.71
7.70
7.69
7.69
7.68
7.67
7.67
7.66
7.66
7.64
7.62
7.57
7.55
7.28
7.26
2.93
2.77
CDCl3, 400 MHz
3r
0.95
0.97
2.96
18.00
1.04
2.96
3.06
2.95
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

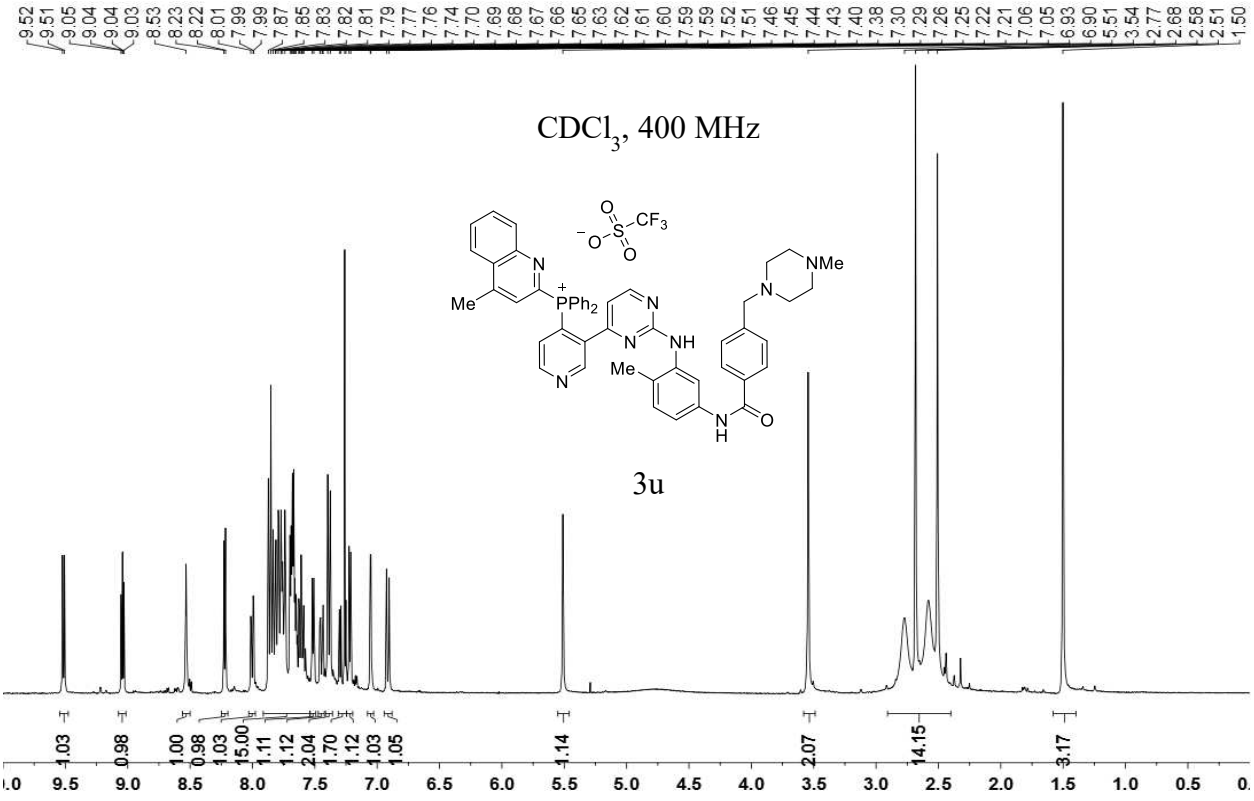

164.27
158.01
157.91
150.92
150.81
148.82
148.71
148.58
148.35
143.24
142.04
140.23
137.66
136.80
136.79
136.07
136.04
134.63
134.53
132.23
131.83
130.75
130.62
130.52
130.29
129.85
128.87
128.78
128.75
128.45
128.33
128.04
126.35
125.86
125.78
125.59
125.24
125.02
124.97
124.31
123.07
122.38
121.83
118.64
115.75
114.88
77.32
77.20
77.00
76.68
44.14
19.06
19.04
CDCl3, 100 MHz
3r
224 216 208 200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

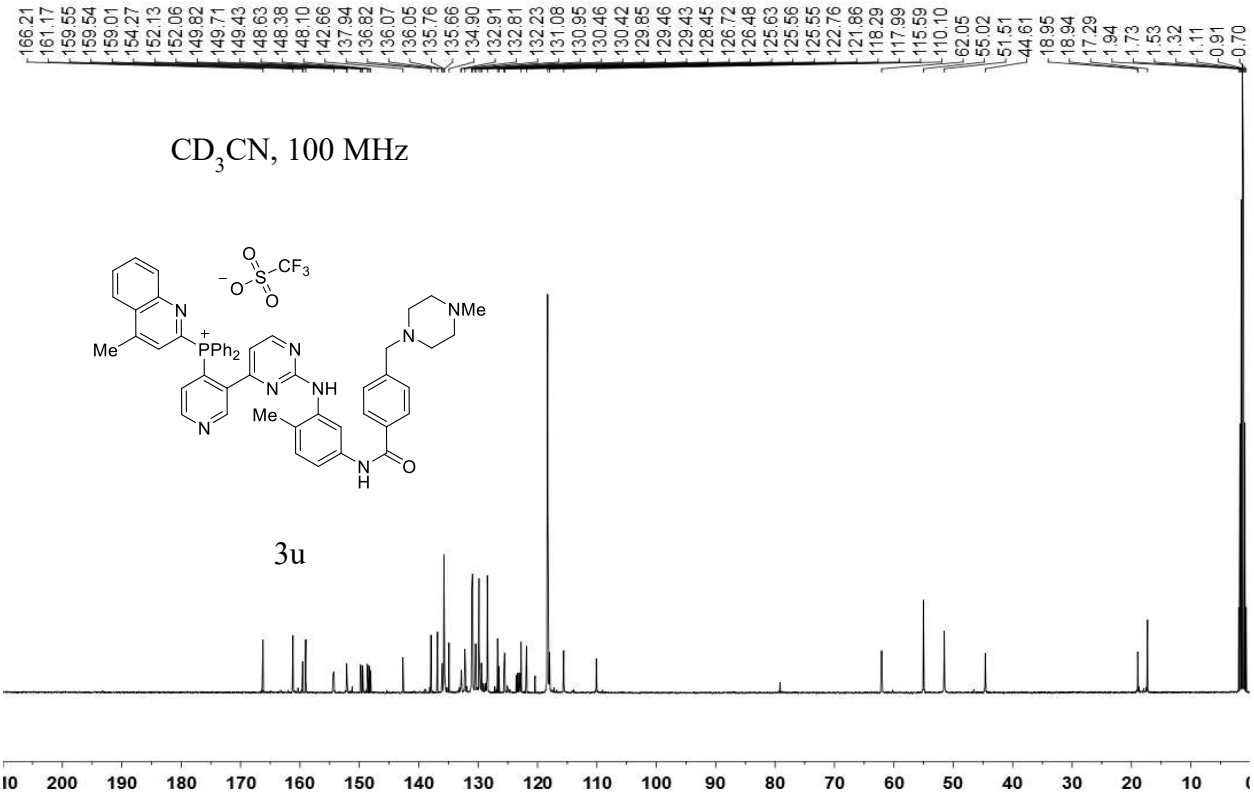

8.32
8.30
8.02
8.01
7.82
7.82
7.80
7.79
7.77
7.75
7.75
7.70
7.70
7.69
7.69
7.68
7.13
7.12
7.11
7.10
7.10
7.09
7.09
7.08
7.06
7.01
6.99
6.94
6.92
6.90
4.16
4.15
4.13
4.11
1.49
1.47
1.45
CDCl3, 400 MHz
Cl
Cl
N
O
PPh2
N
EtO
F
O
S
CF3
O
O
3s
0.97
1.02
14.00
3.10
0.99
2.01
1.97
2.96
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

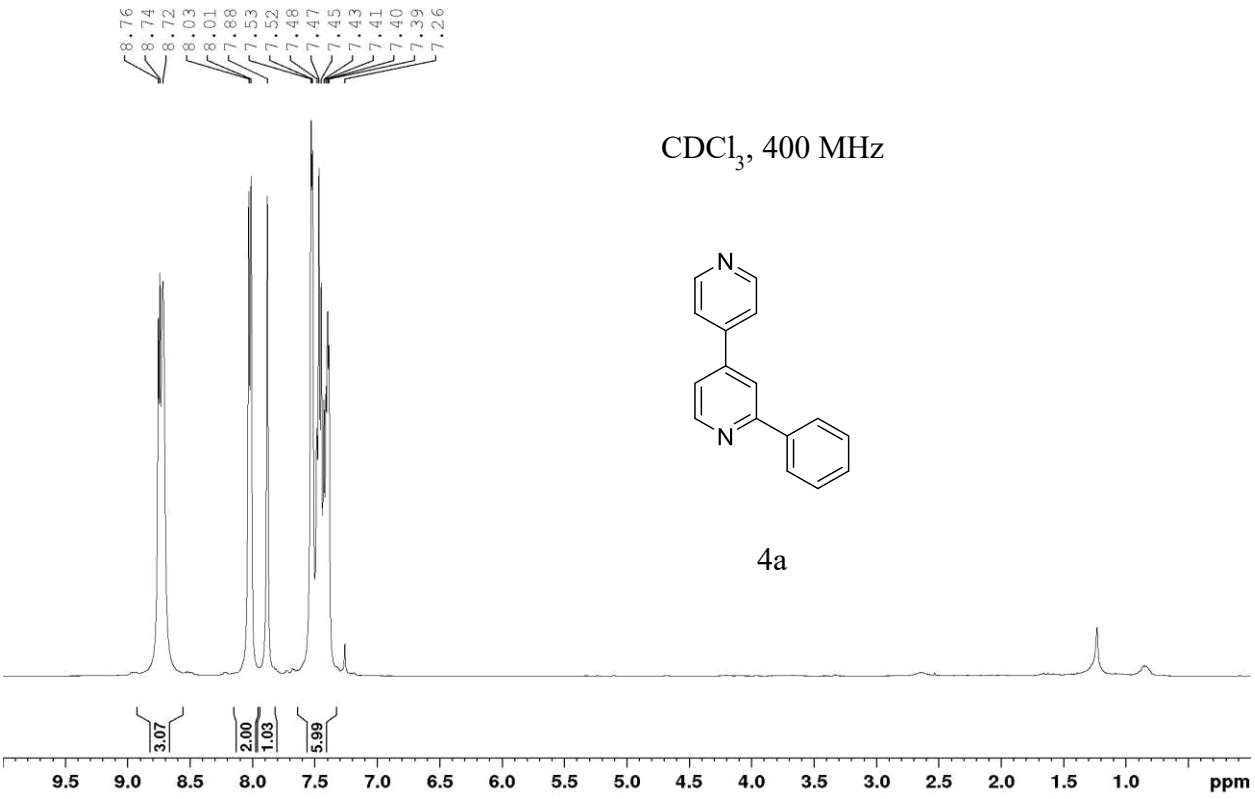

163.37
163.23
161.49
159.05
151.81
151.56
149.36
149.11
148.88
148.15
148.12
147.71
145.15
143.98
136.97
135.55
135.52
134.73
134.63
132.24
131.96
131.68
131.10
131.09
130.33
130.20
129.13
127.99
122.82
122.73
122.45
122.23
121.57
121.55
119.04
118.18
118.15
117.21
116.98
116.95
116.08
111.06
110.80
106.07
105.78
65.51
13.93
CDCl3, 100 MHz
Cl
Cl
N
O
PPh2
N
EtO
F
O
S
CF3
O
O
3s
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
ppm


7.95 7.95 7.85 7.85 7.84 7.84 7.83 7.83 7.82 7.81 7.81 7.81 7.80 7.80 7.79 7.78 7.78 7.75 7.75 7.74 7.73 7.73 7.72 7.71 7.71 7.71 7.69 7.69 7.60 7.60 7.60 7.59 7.58 7.57 7.57 7.29 7.28 7.25
3.17
2.74
2.60
CDCl3, 400 MHz
Me
PPh2
N
Cl
Me
Me−S=O
O
3t
0.95
7.97
9.00
2.90
1.46
0.56
2.86
2.87
2.93
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


152.11 152.04 148.29 148.18 147.99 147.97 147.72 147.44 147.20 146.47 146.15 141.55 141.15 138.54 135.30 135.29 135.15 135.12 134.90 134.80 133.40 133.37 131.95 131.71 130.76 130.66 130.23 130.10 130.04 129.75 129.74 129.29 128.43 128.36 128.13 128.10 125.62 124.45 123.66 123.39 122.43 119.75 119.23 118.87
44.14
24.62
18.84
18.83
CDCl3, 100 MHz
Me
PPh2
N
Cl
Me
Me−S=O
O
3t
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

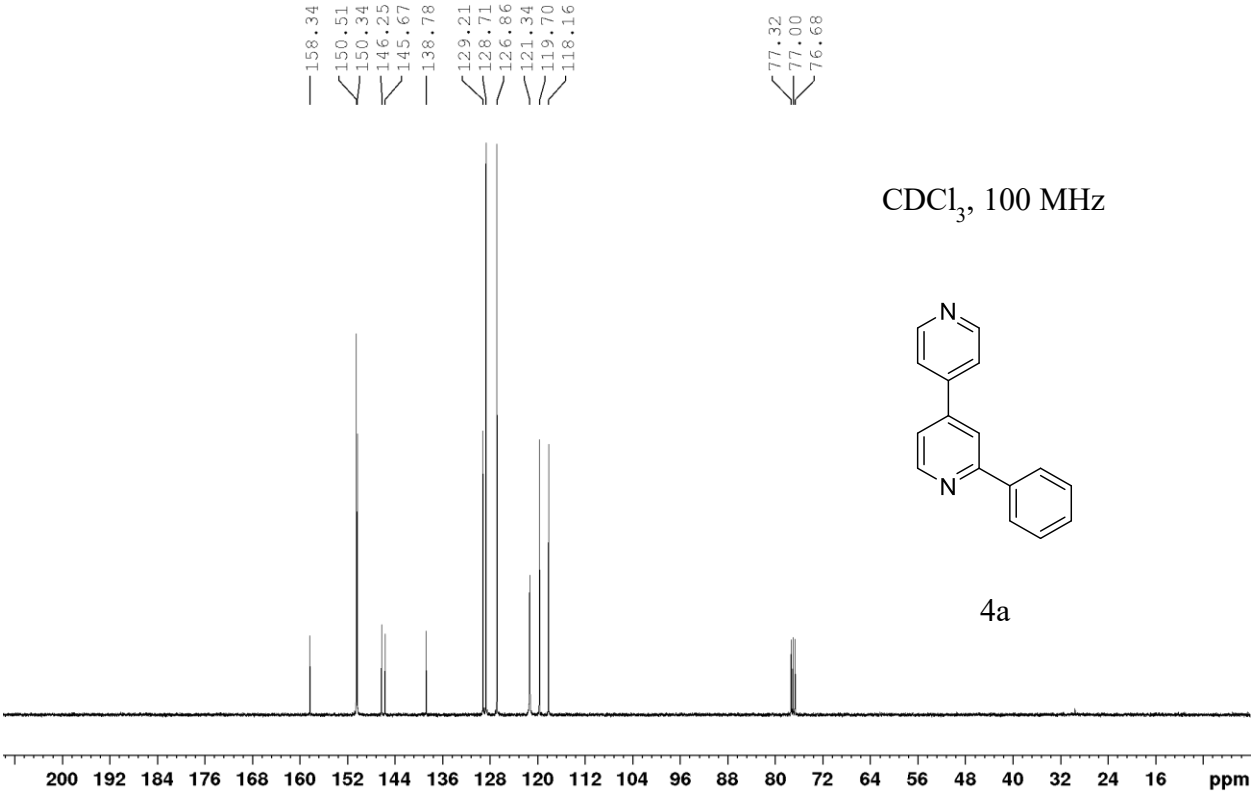

CDCl3, 400 MHz
3u


CD3CN, 100 MHz
3u



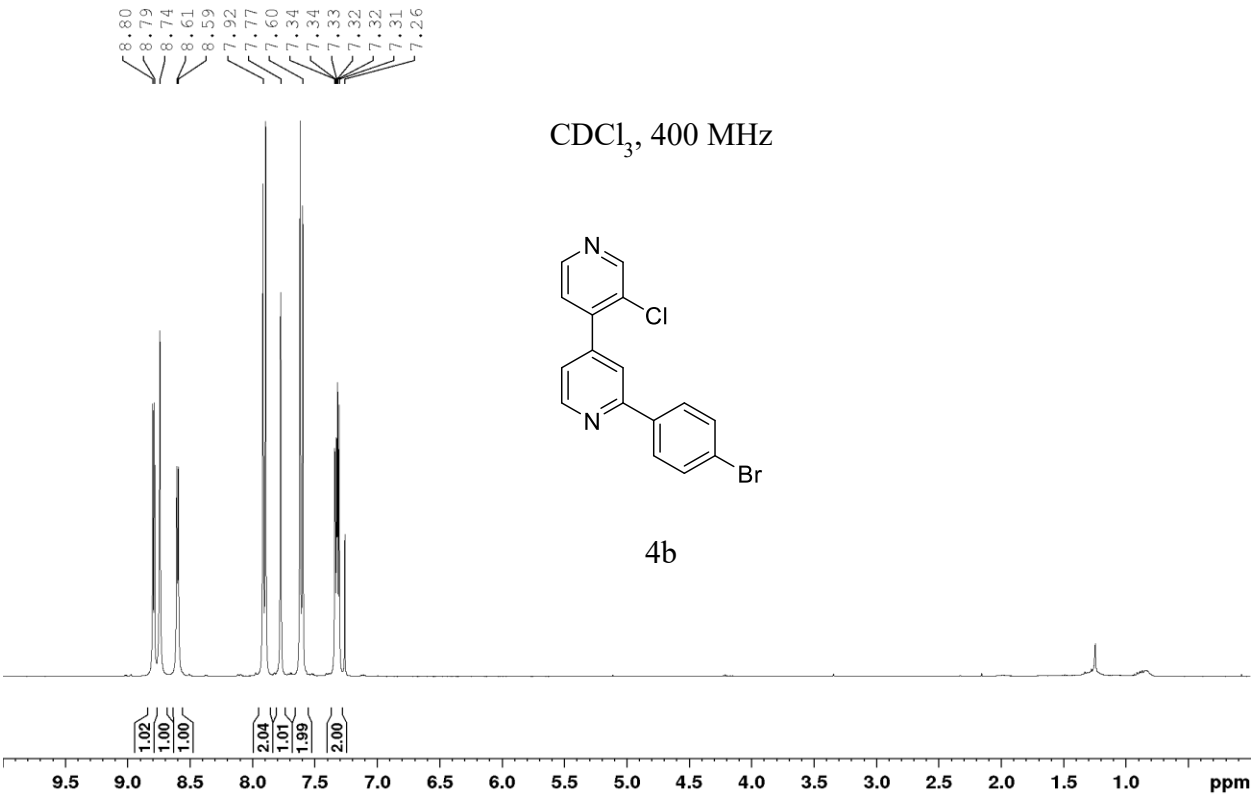
$CDCl_3$, 400 MHz

4a



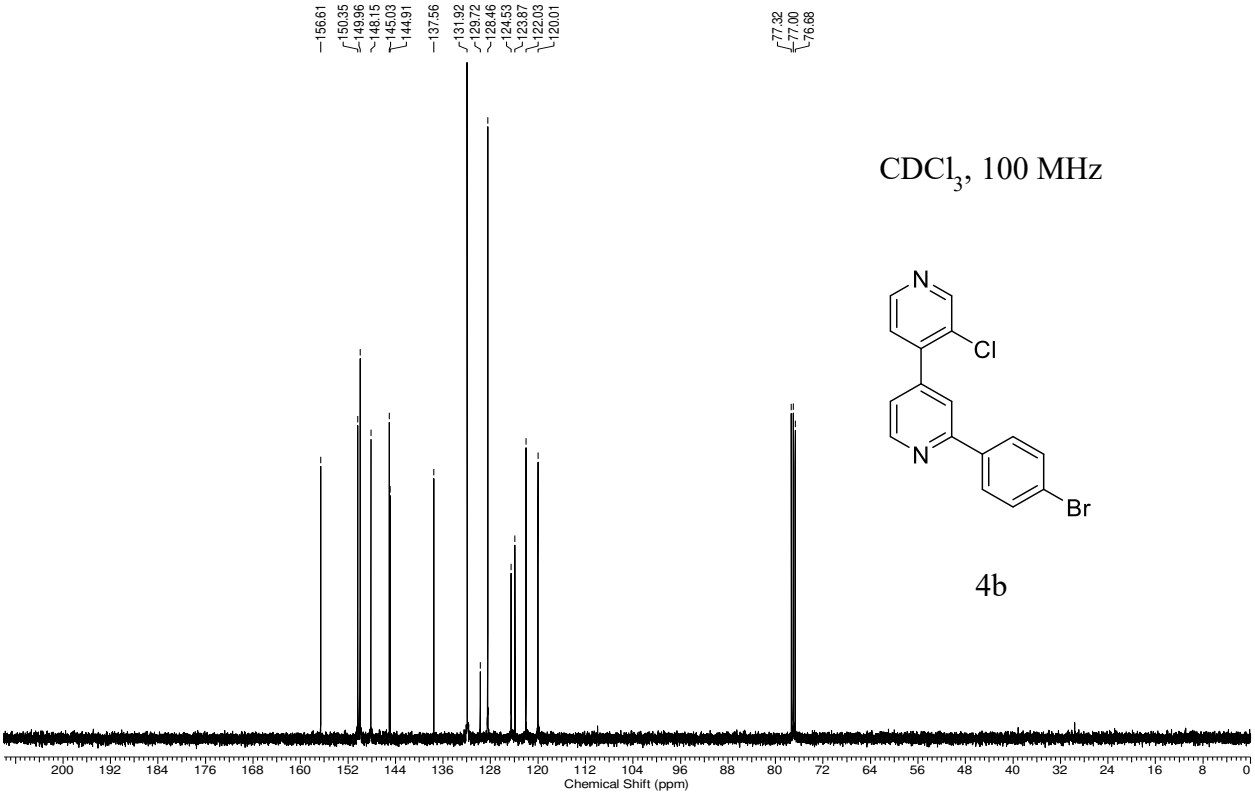
$CDCl_3$, 100 MHz

4a



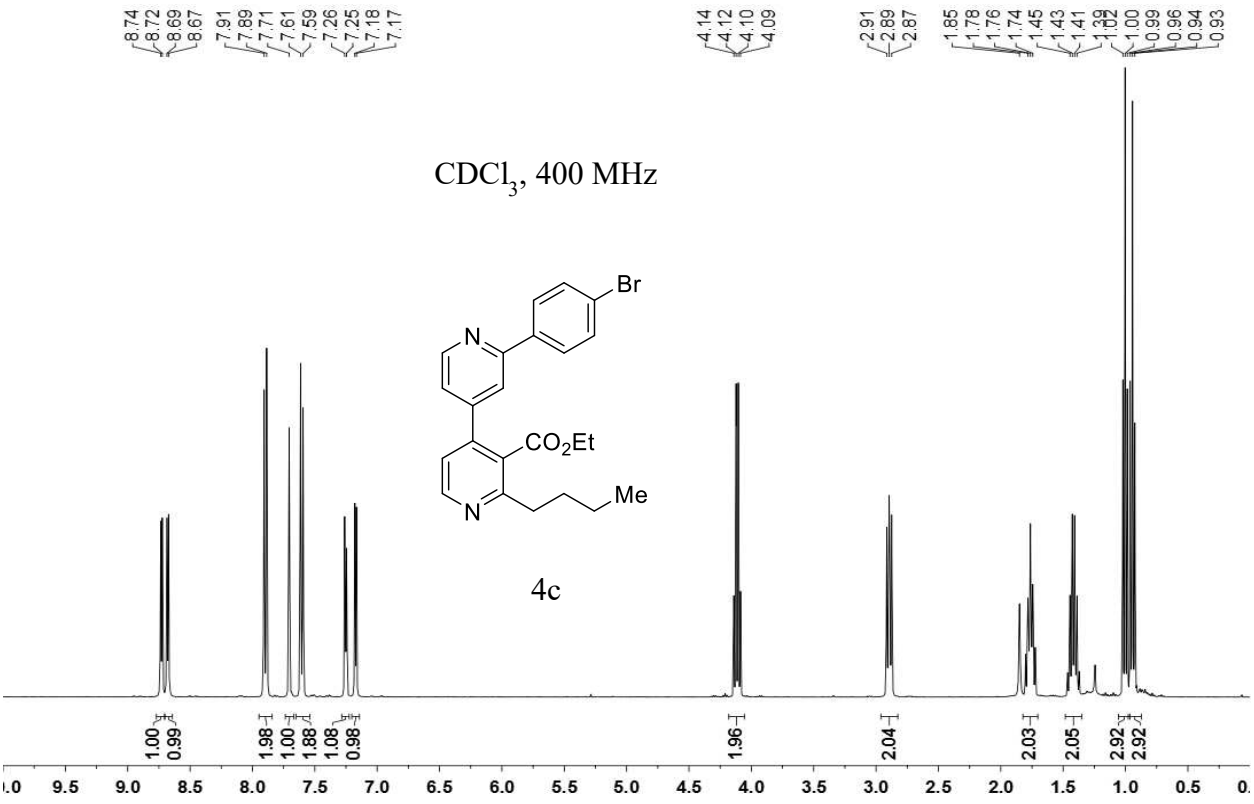
$CDCl_3$, 400 MHz

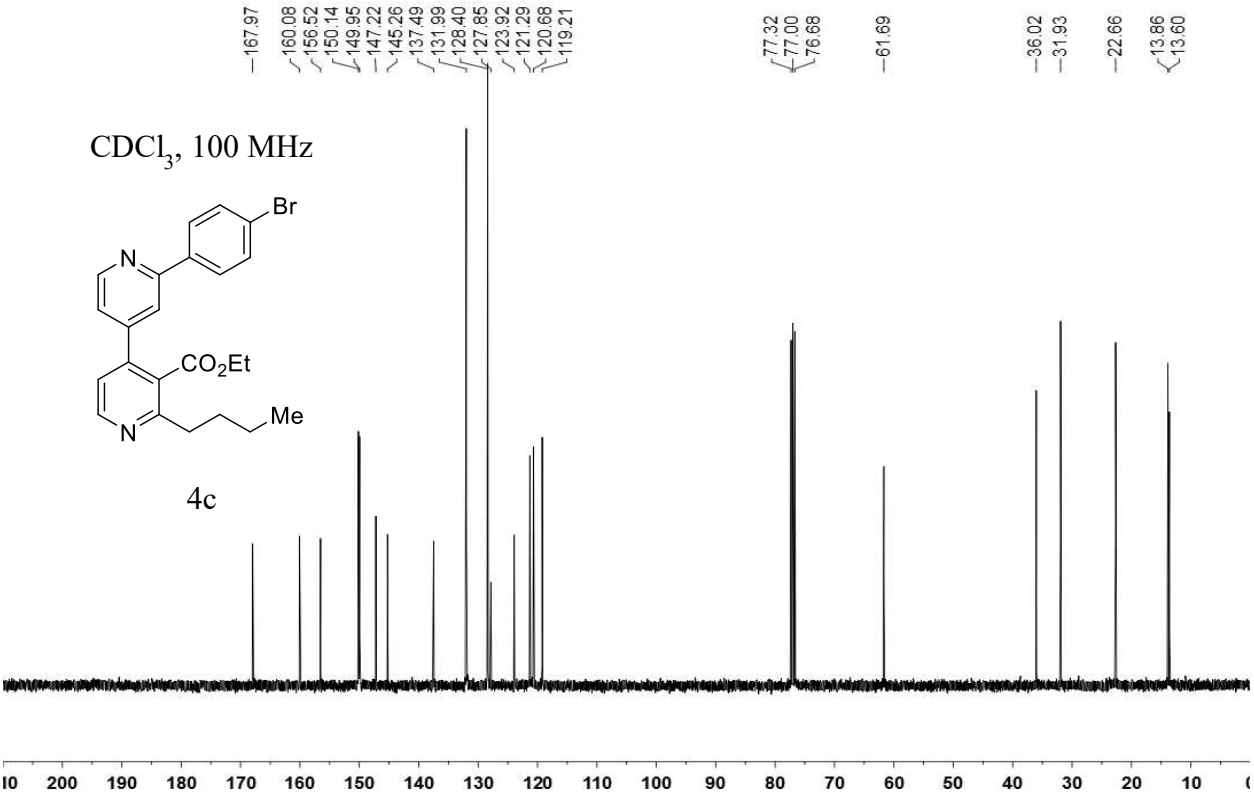
4b

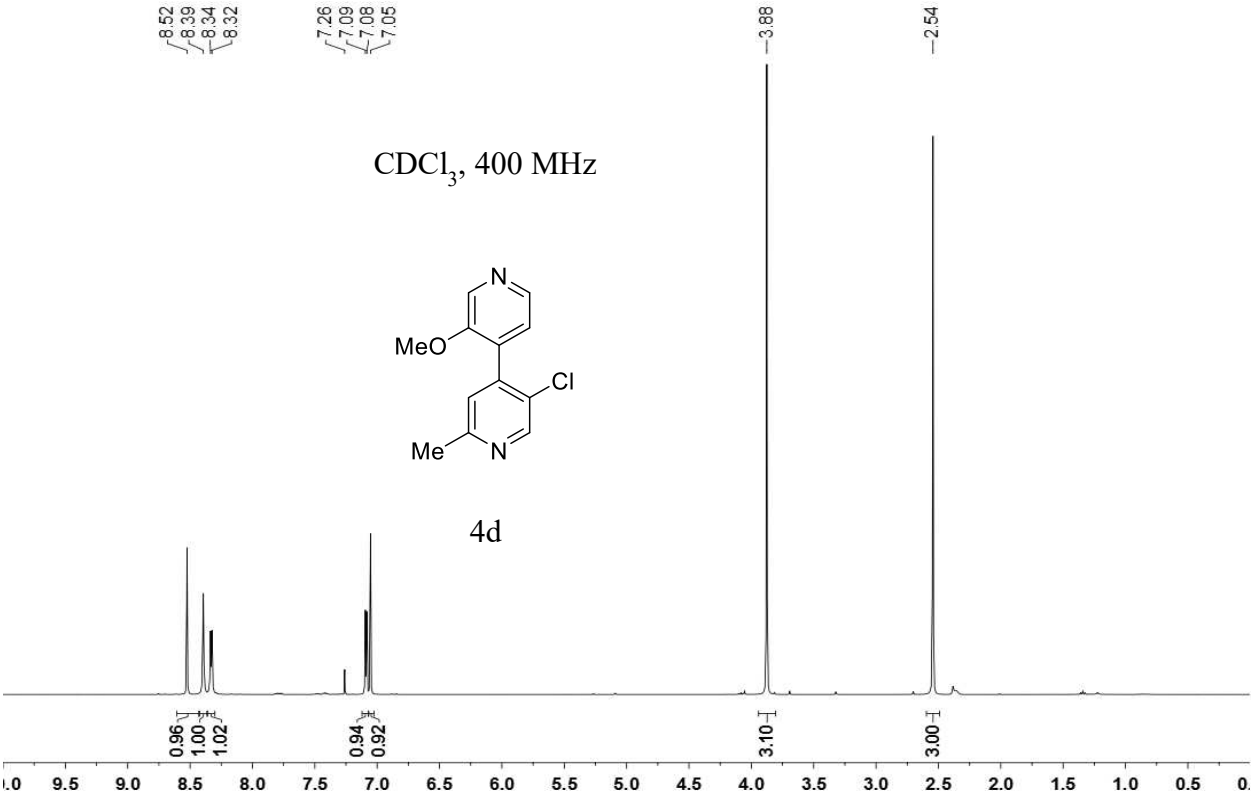


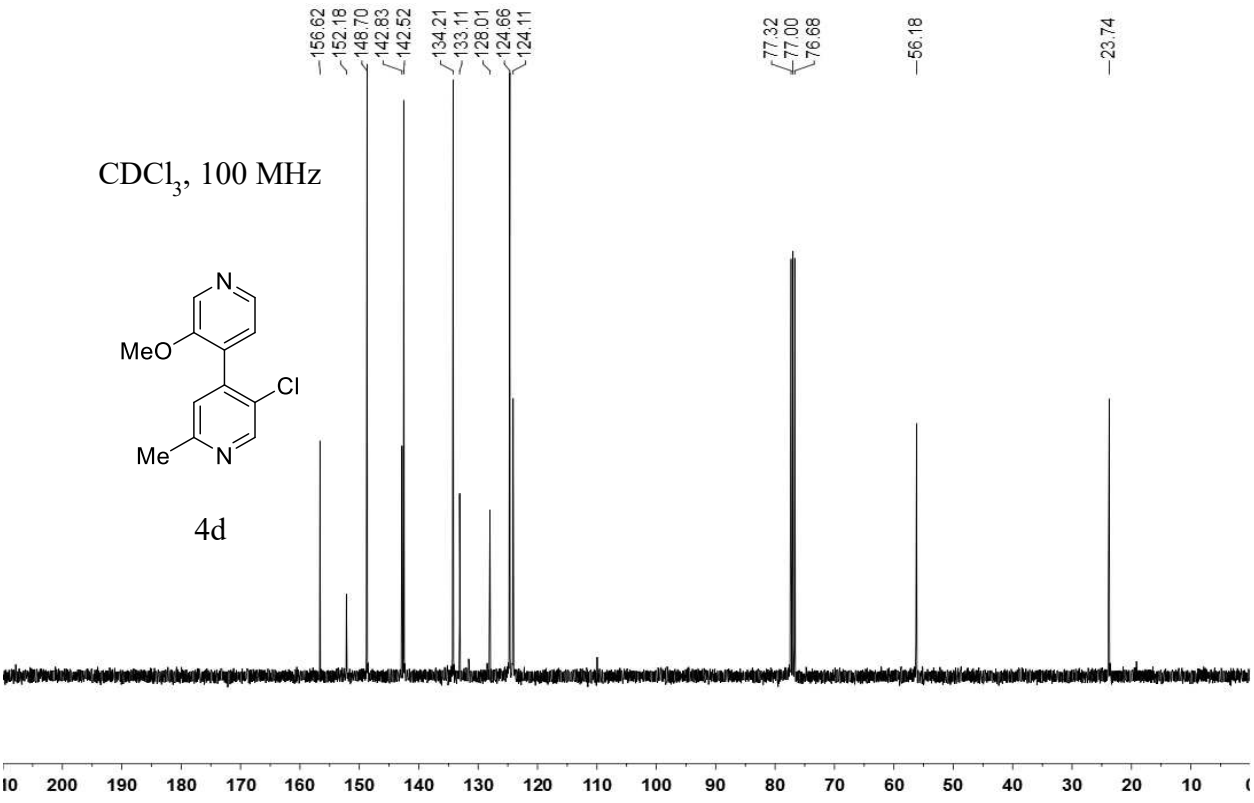
$CDCl_3$, 100 MHz

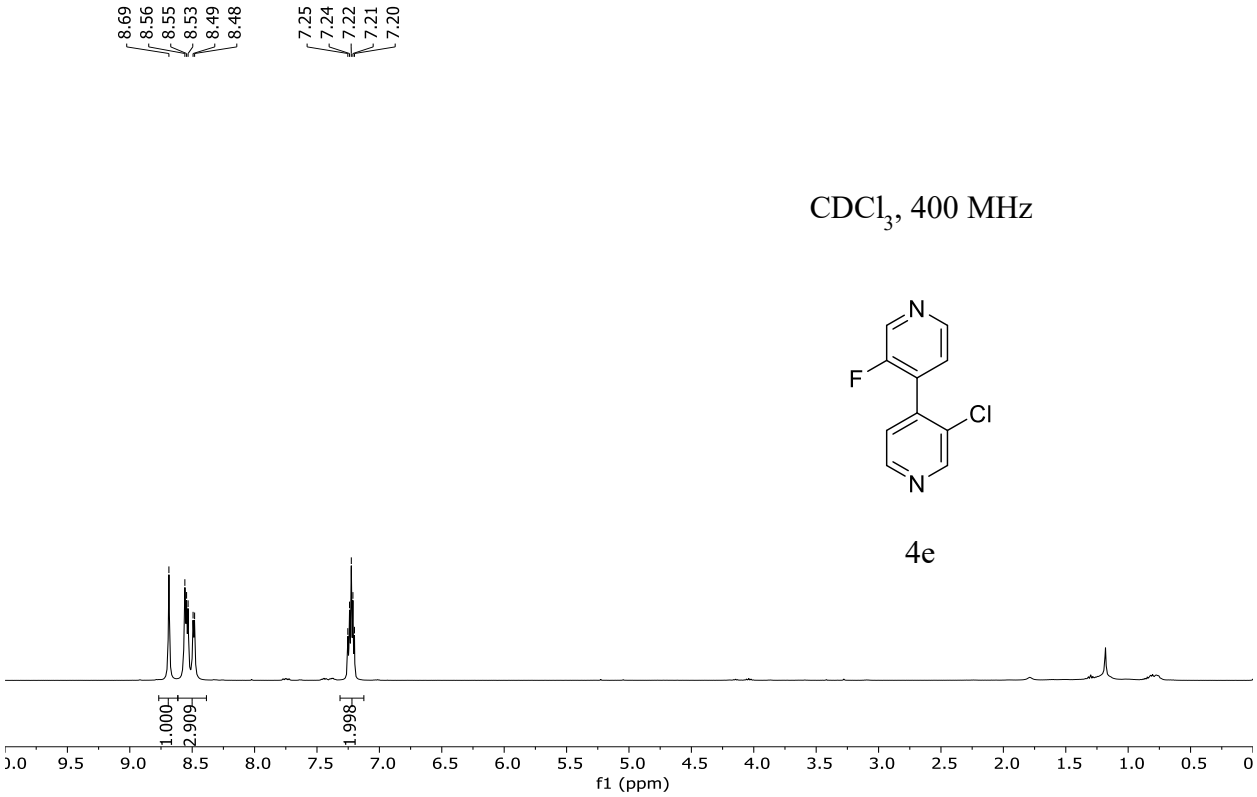
4b

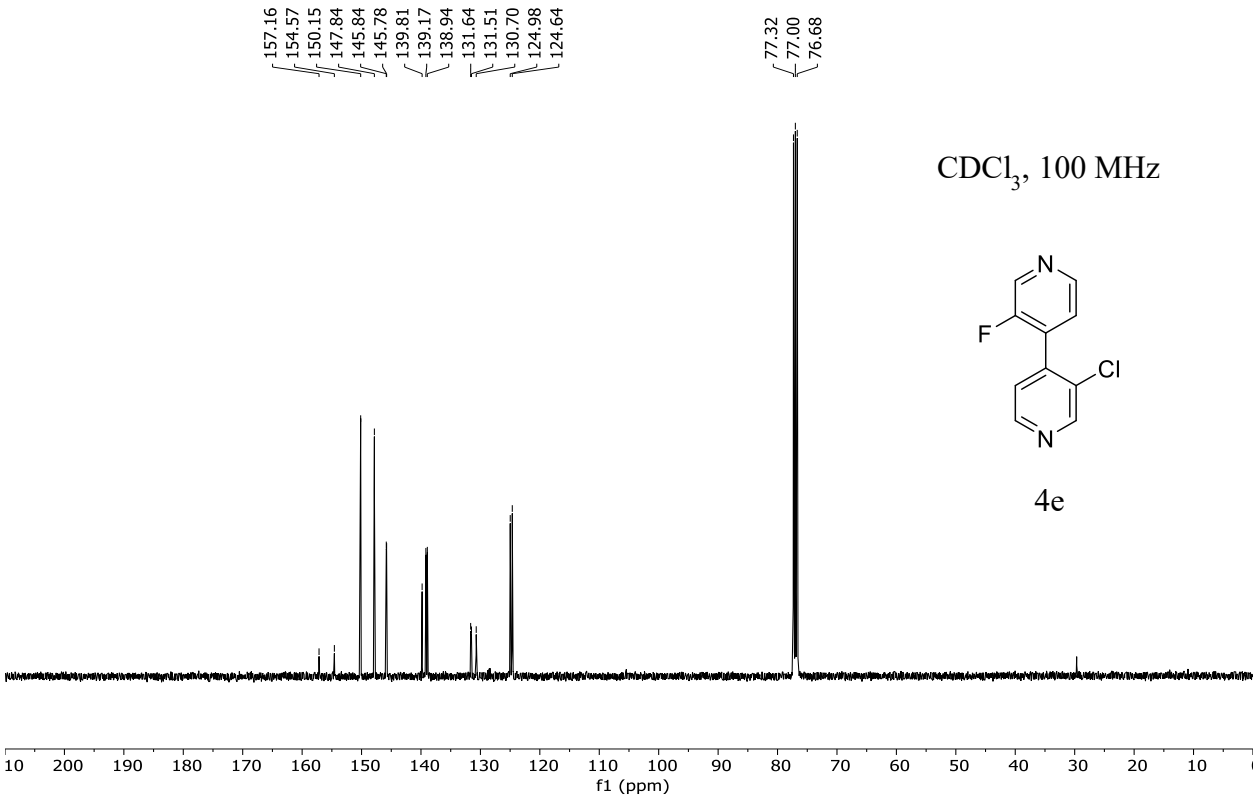

8.74
8.72
8.69
8.67
7.91
7.89
7.71
7.61
7.59
7.26
7.25
7.18
7.17
4.14
4.12
4.10
4.09
2.91
2.89
2.87
1.85
1.78
1.76
1.74
1.45
1.43
1.41
1.00
0.99
0.96
0.94
0.93
CDCl3, 400 MHz
Br
N
CO2Et
Me
N
4c
1.00
0.99
1.98
1.00
1.88
1.08
0.98
1.96
2.04
2.03
2.05
2.92
2.92
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

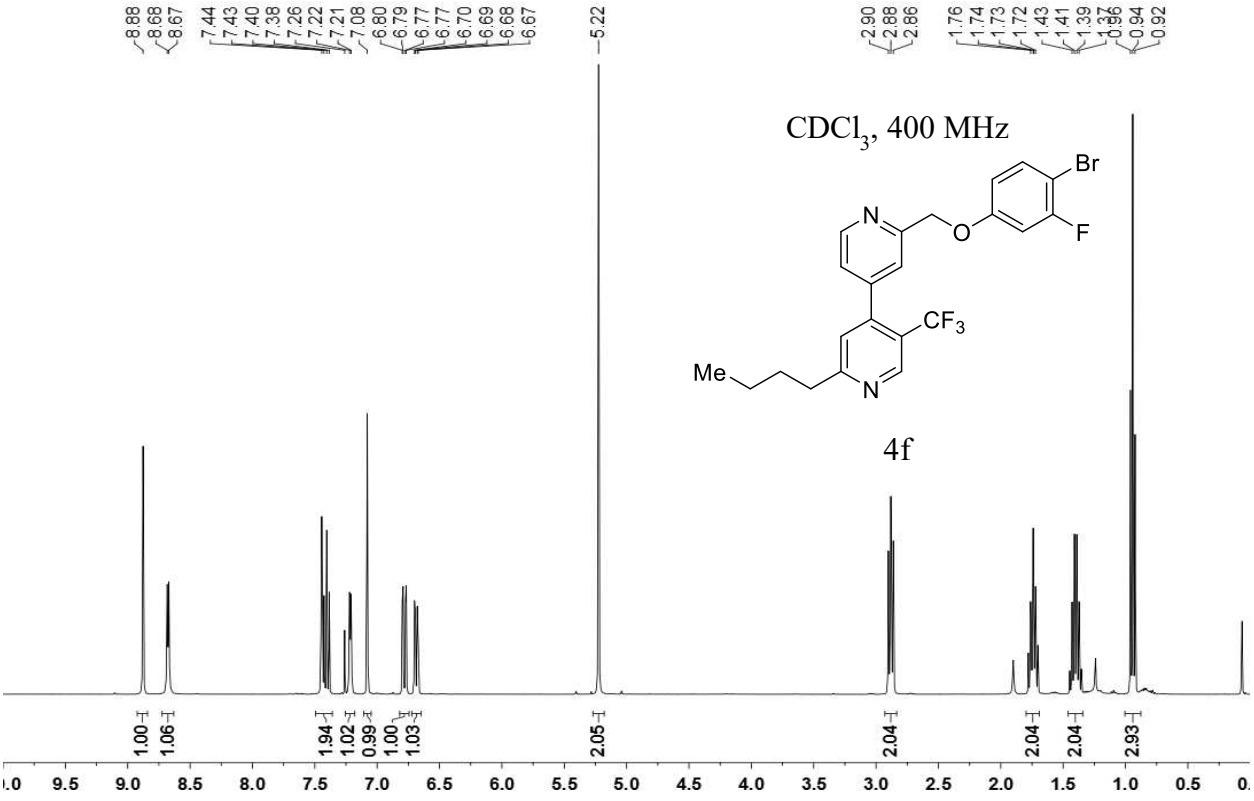

167.97
160.08
156.52
150.14
149.95
147.22
145.26
137.49
131.99
128.40
127.85
123.92
121.29
120.68
119.21
77.32
77.00
76.68
61.69
36.02
31.93
22.66
13.86
13.60
CDCl3, 100 MHz
Br
N
CO2Et
Me
N
4c
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

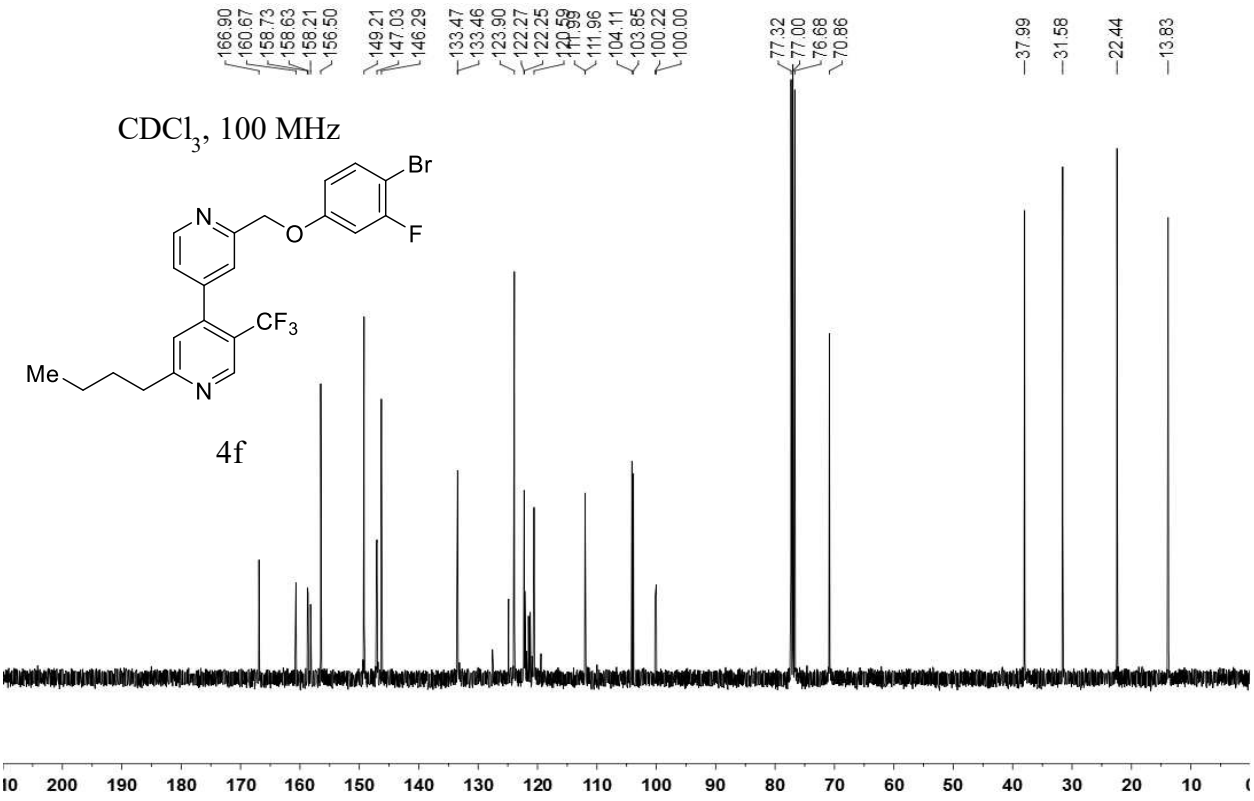

8.52
8.39
8.34
8.32
7.26
7.09
7.08
7.05
3.88
2.54
CDCl3, 400 MHz
N
MeO
Cl
Me
N
4d
0.96
1.00
1.02
0.94
0.92
3.10
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

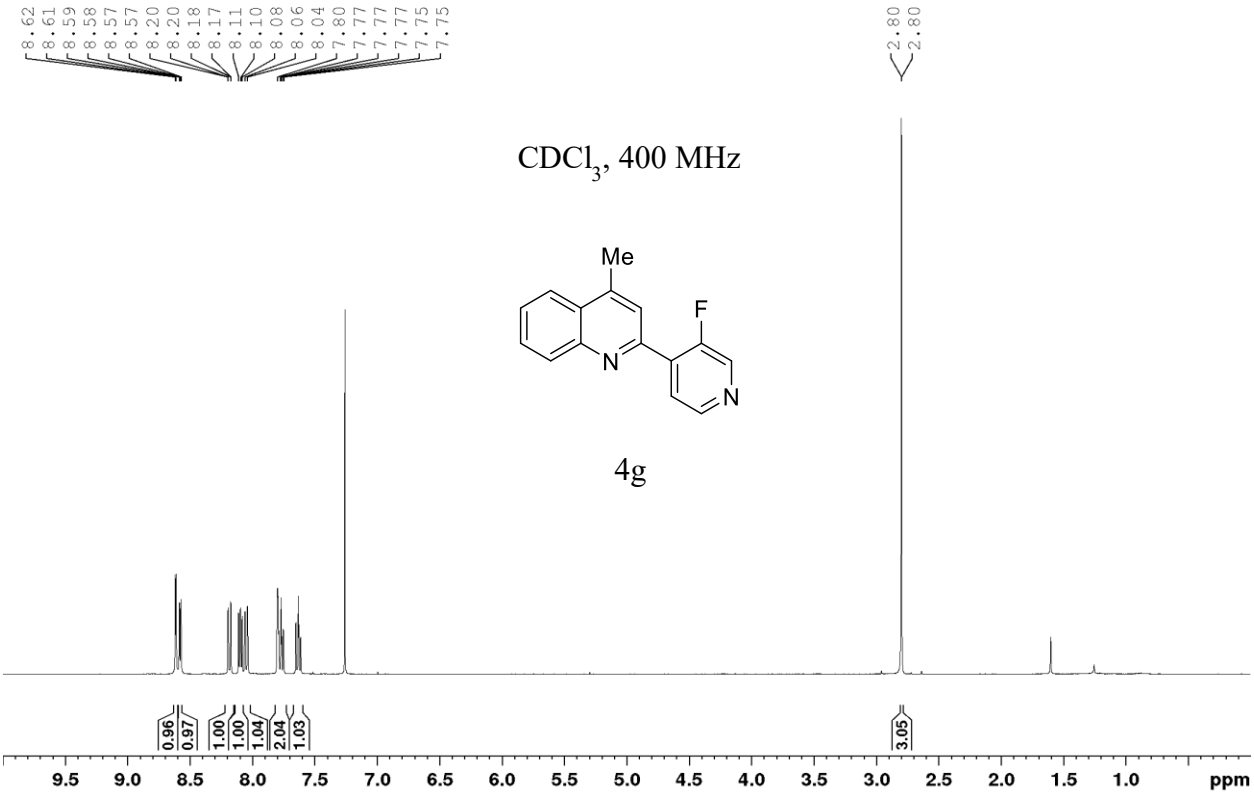

156.62
152.18
148.70
142.83
142.52
134.21
133.11
128.01
124.66
124.11
77.32
77.00
76.68
56.18
23.74
CDCl3, 100 MHz
N
MeO
Cl
Me
N
4d
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

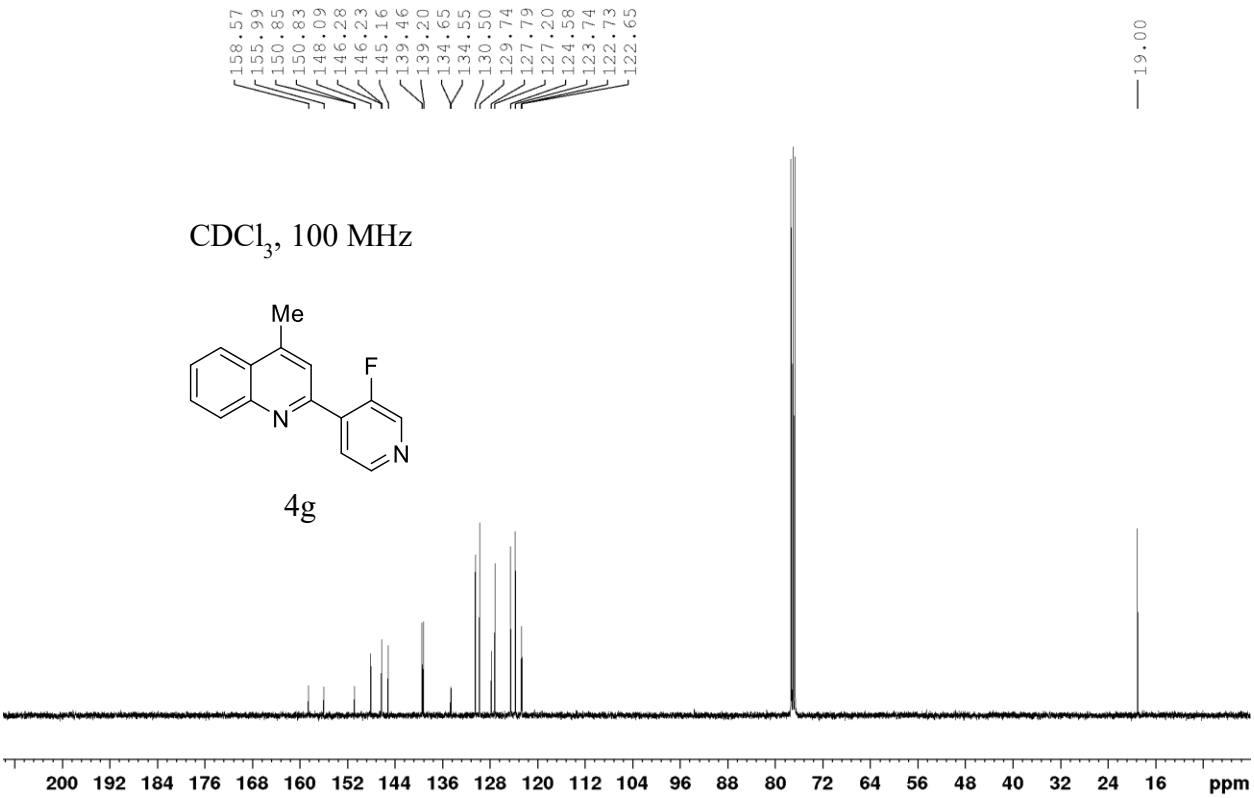

8.69
8.56
8.55
8.53
8.49
8.48
7.25
7.24
7.22
7.21
7.20
CDCl3, 400 MHz
N
F
Cl
N
4e
1.000
2.909
1.998
f1 (ppm)

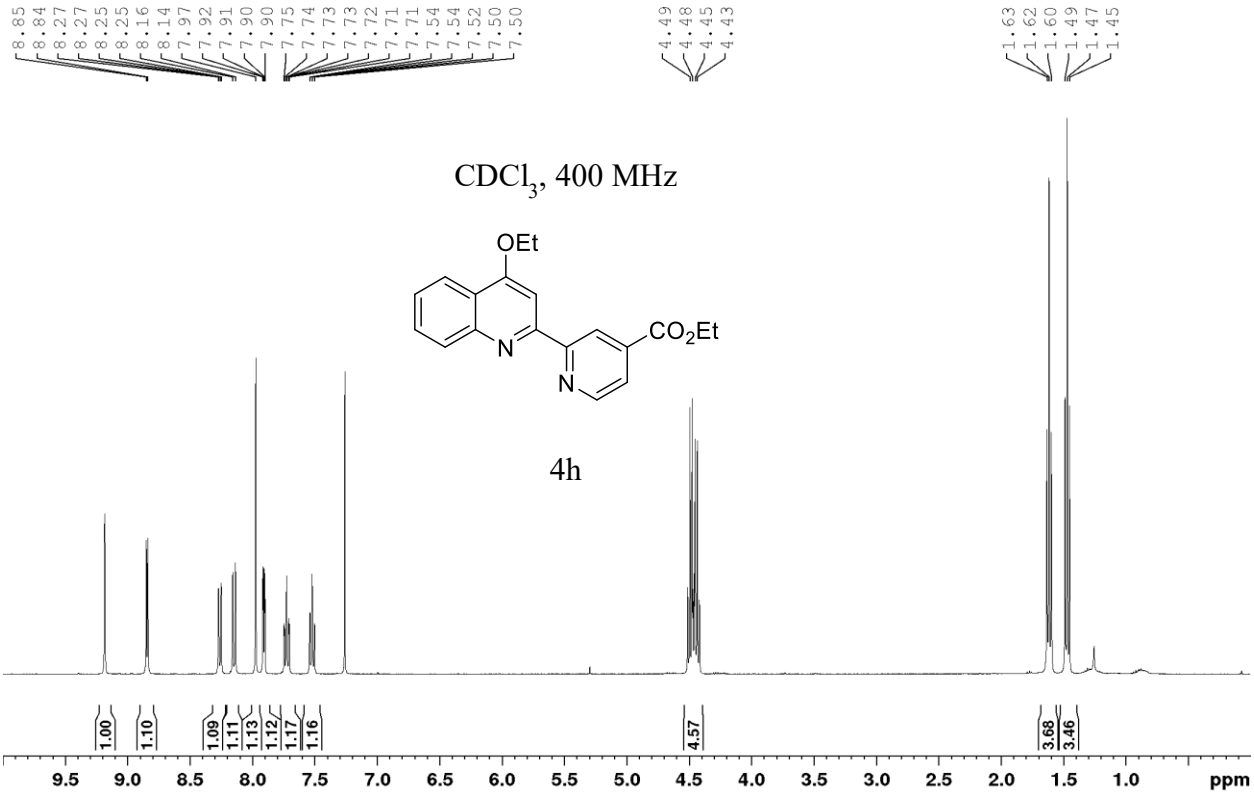

157.16
154.57
150.15
147.84
145.84
145.78
139.81
139.17
138.94
131.64
131.51
130.70
124.98
124.64
77.32
77.00
76.68
CDCl3, 100 MHz
N
F
Cl
N
4e
f1 (ppm)

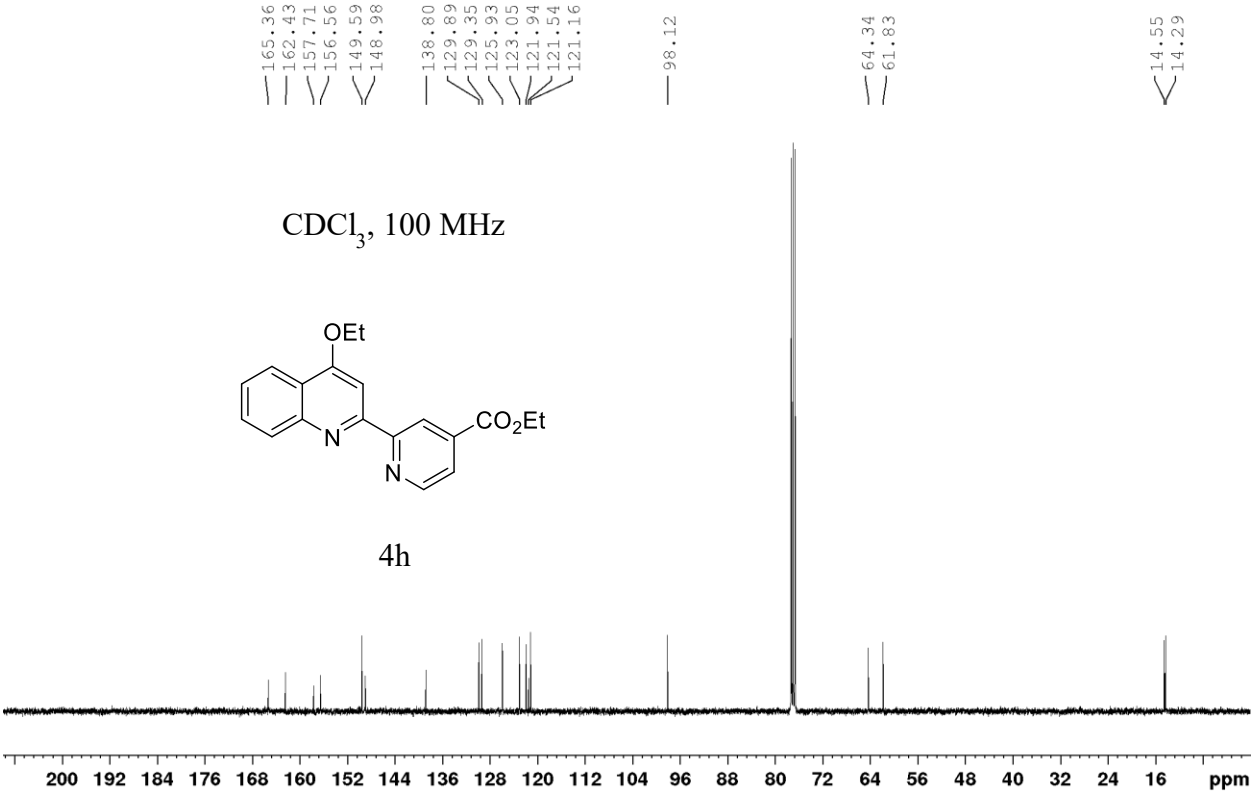

8.88
8.68
8.67
7.44
7.43
7.40
7.38
7.26
7.22
7.21
7.08
6.80
6.79
6.77
6.77
6.70
6.69
6.68
6.67
5.22
2.90
2.88
2.86
1.76
1.74
1.73
1.72
1.43
1.41
1.39
0.96
0.94
0.92
CDCl3, 400 MHz
Br
F
N
O
CF3
Me
N
4f
1.00
1.06
1.94
1.02
0.99
1.00
1.03
2.05
2.04
2.04
2.04
2.93

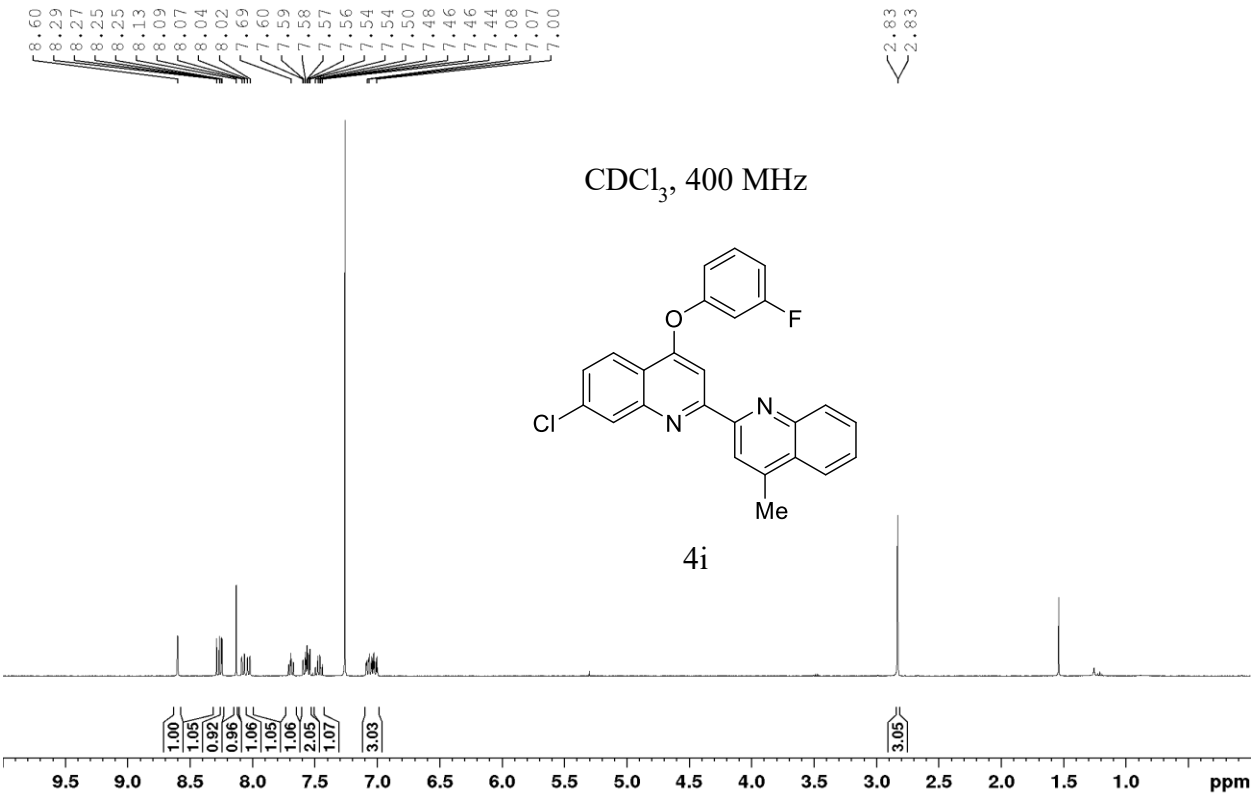

166.90
160.67
158.73
158.63
158.21
156.50
149.21
147.03
146.29
133.47
133.46
123.90
122.27
122.25
111.96
104.11
103.85
100.22
100.00
77.32
77.00
76.68
70.86
37.99
31.58
22.44
13.83
CDCl3, 100 MHz
Br
F
N
O
CF3
Me
N
4f

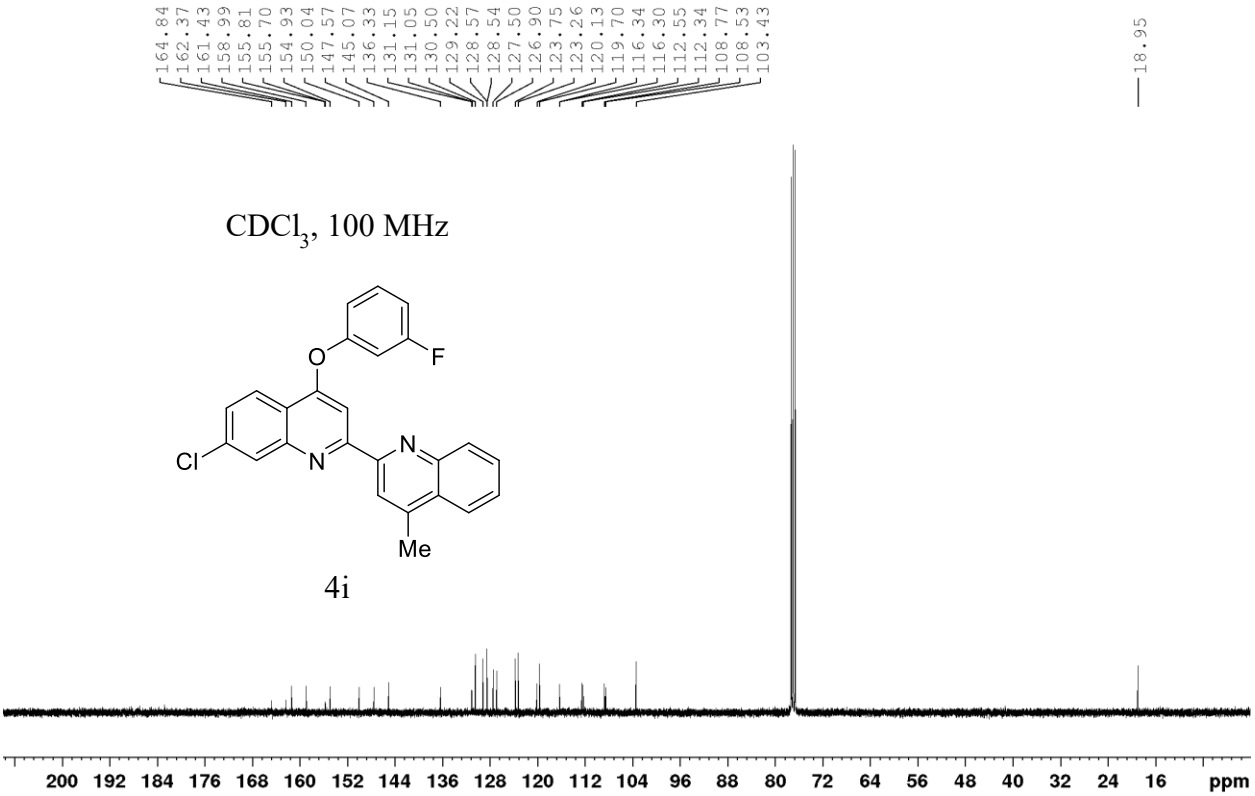

8.62
8.61
8.59
8.58
8.57
8.57
8.20
8.20
8.18
8.17
8.11
8.10
8.08
8.06
8.04
7.80
7.77
7.77
7.77
7.75
7.75
2.80
2.80
CDCl3, 400 MHz
Me
F
N
N
4g
0.96
0.97
1.00
1.00
1.04
2.04
1.03
3.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

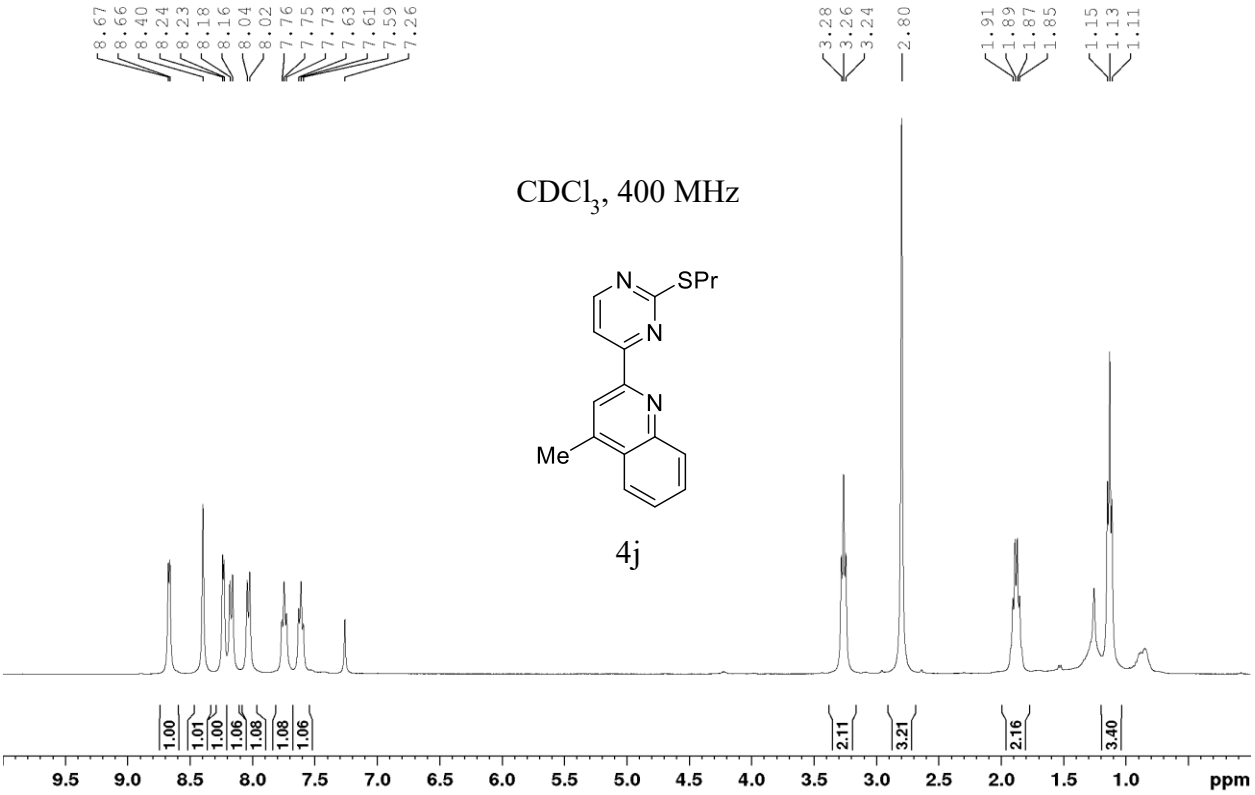

158.57
155.99
150.85
150.83
148.09
146.28
146.23
145.16
139.46
139.20
134.65
134.55
130.50
129.74
127.79
127.20
124.58
123.74
122.73
122.65
19.00
CDCl3, 100 MHz
Me
F
N
N
4g
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

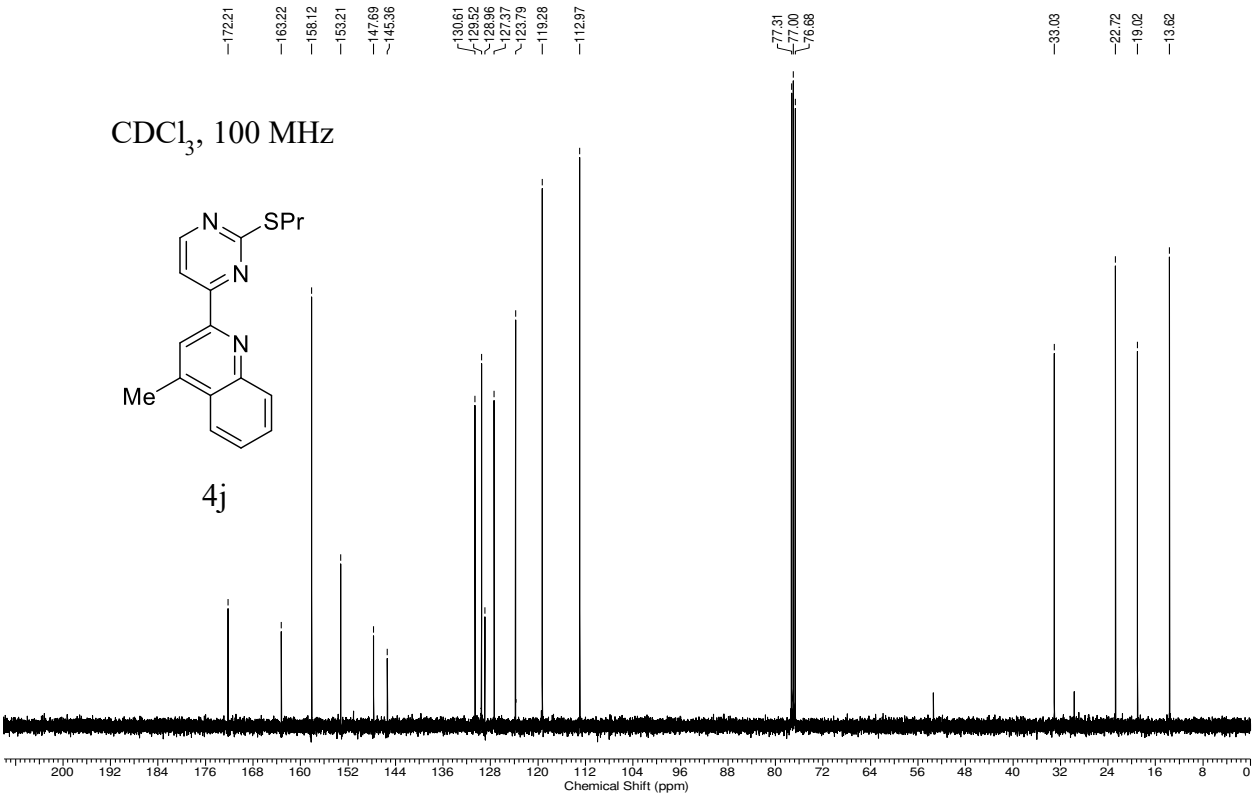

8.85
8.84
8.27
8.27
8.25
8.25
8.16
8.14
7.97
7.92
7.91
7.90
7.90
7.75
7.74
7.73
7.73
7.72
7.71
7.71
7.54
7.54
7.52
7.50
7.50
4.49
4.48
4.45
4.43
1.63
1.62
1.60
1.49
1.47
1.45
CDCl3, 400 MHz
OEt
CO2Et
N
N
4h
1.00
1.10
1.09
1.11
1.13
1.12
1.17
1.16
4.57
3.68
3.46
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

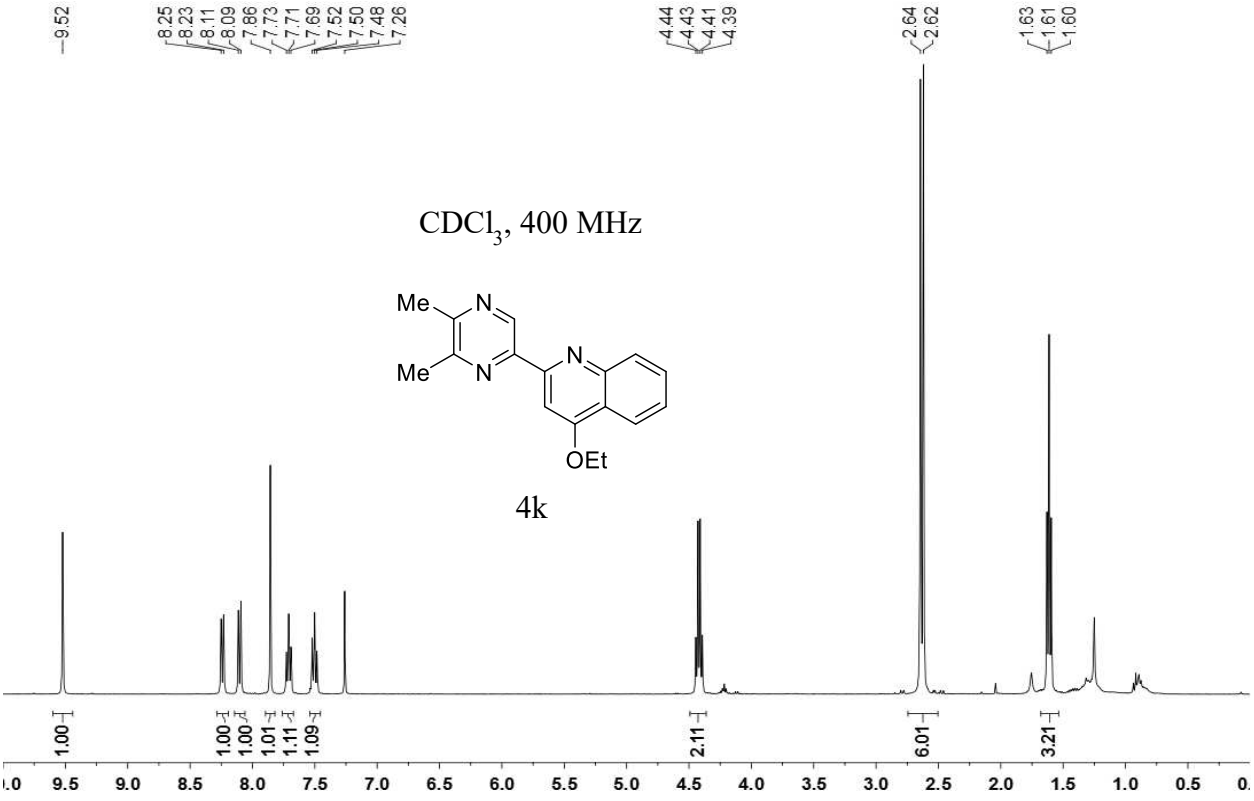

165.36
162.43
157.71
156.56
149.59
148.98
138.80
129.89
129.35
125.93
123.05
121.94
121.54
121.16
98.12
64.34
61.83
14.55
14.29
CDCl3, 100 MHz
OEt
CO2Et
N
N
4h
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
ppm


8.60
8.29
8.27
8.25
8.25
8.13
8.09
8.07
8.04
8.02
7.69
7.60
7.59
7.58
7.57
7.56
7.54
7.54
7.50
7.48
7.46
7.46
7.44
7.08
7.07
7.00
2.83
2.83
CDCl3, 400 MHz
O
F
Cl
N
N
Me
4i
1.00
1.05
0.92
0.96
1.06
1.05
1.06
2.05
1.07
3.03
3.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm


164.84
162.37
161.43
158.99
155.81
155.70
154.93
150.04
147.57
145.07
136.33
131.15
131.05
130.50
129.22
128.57
128.54
127.50
126.90
123.75
123.26
120.13
119.70
116.34
116.30
112.55
112.34
108.77
108.53
103.43
18.95
CDCl3, 100 MHz
O
F
Cl
N
N
Me
4i
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16
ppm

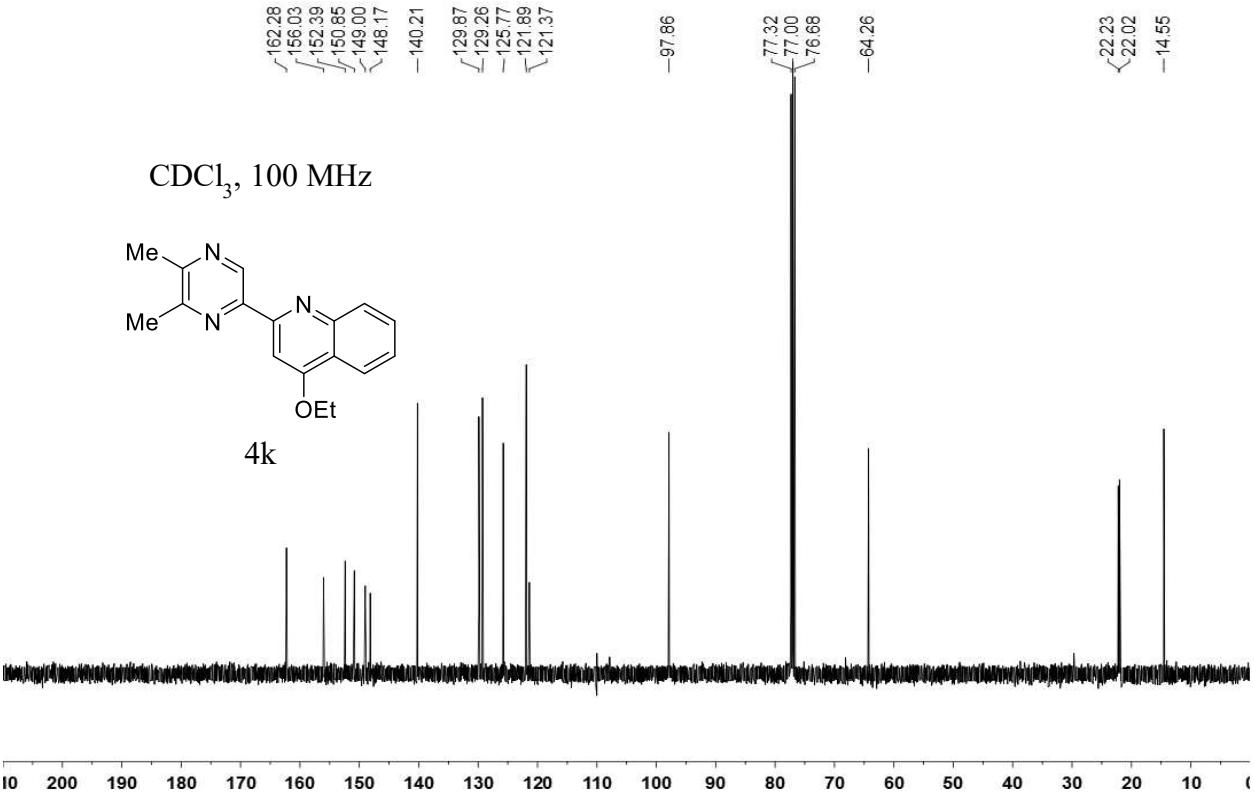

8.67
8.66
8.40
8.24
8.23
8.18
8.16
8.04
8.02
7.76
7.75
7.73
7.63
7.61
7.59
7.26
3.28
3.26
3.24
2.80
1.91
1.89
1.87
1.85
1.15
1.13
1.11
CDCl3, 400 MHz
N
SPr
N
N
Me
4j
1.00
1.01
1.00
1.06
1.08
1.08
1.06
2.11
3.21
2.16
3.40
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


172.21
163.22
158.12
153.21
147.69
145.36
130.61
129.52
128.96
127.37
123.79
119.28
112.97
77.31
77.00
76.68
33.03
22.72
19.02
13.62
CDCl3, 100 MHz
N
SPr
N
N
Me
4j
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)



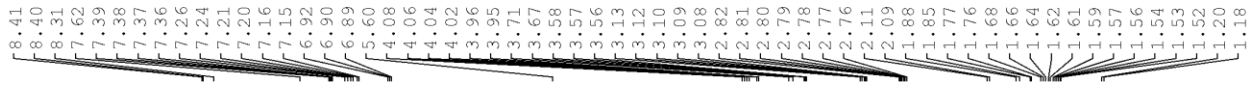
$CDCl_3$, 400 MHz

4k

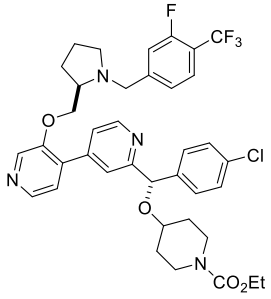


$CDCl_3$, 100 MHz

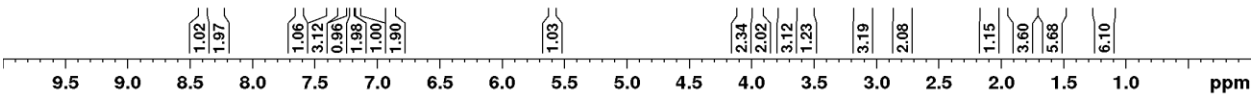
4k

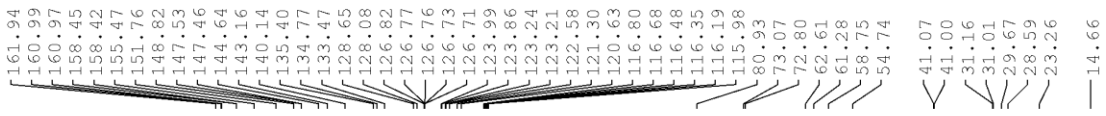


$CDCl_3$, 400 MHz

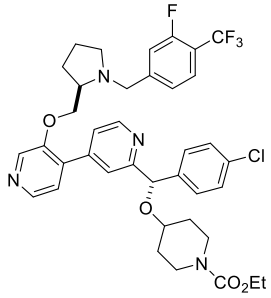


41

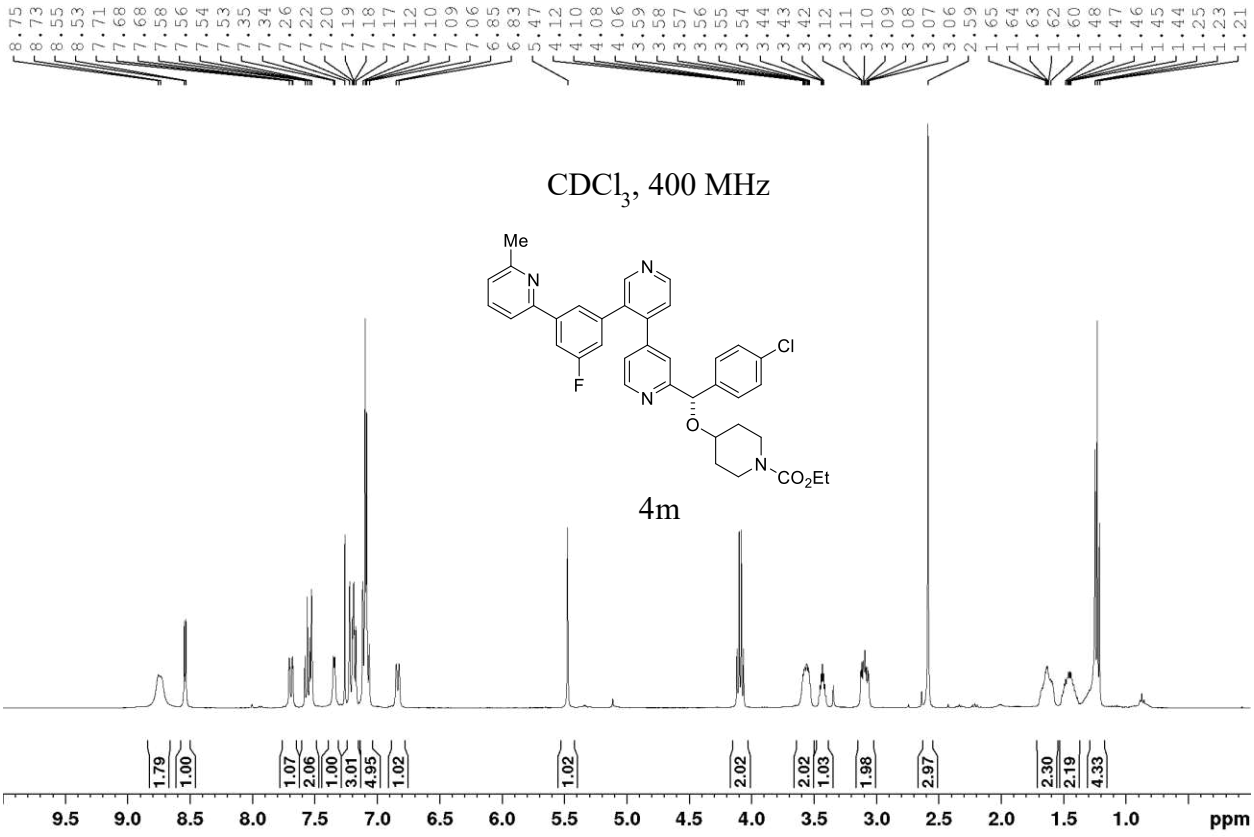


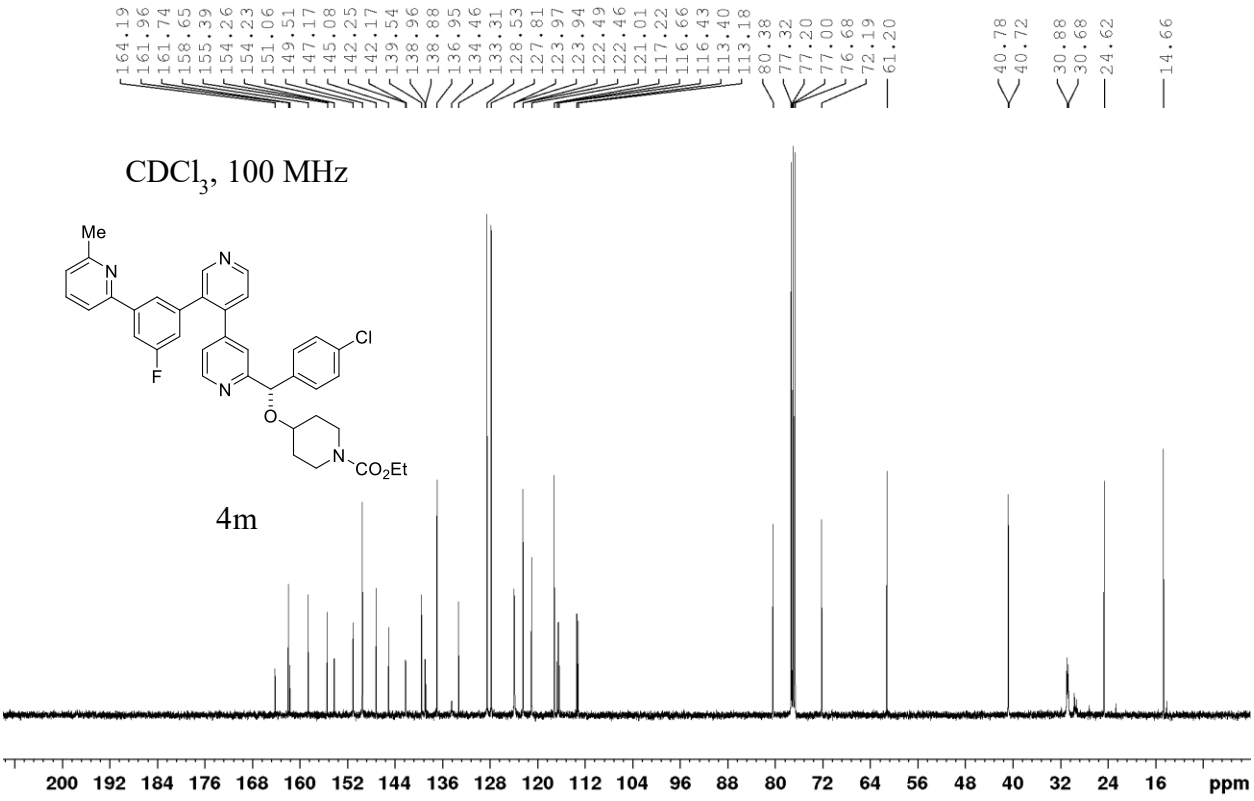


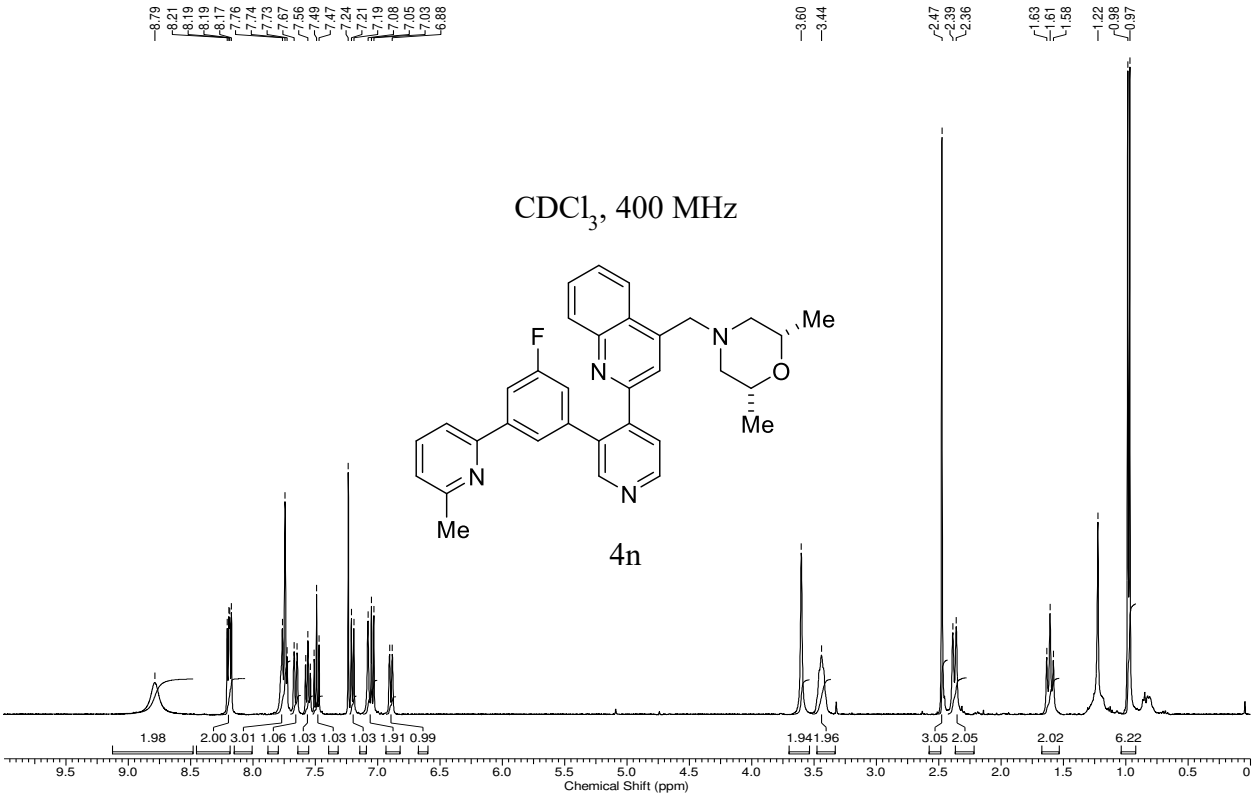
$CDCl_3$, 100 MHz

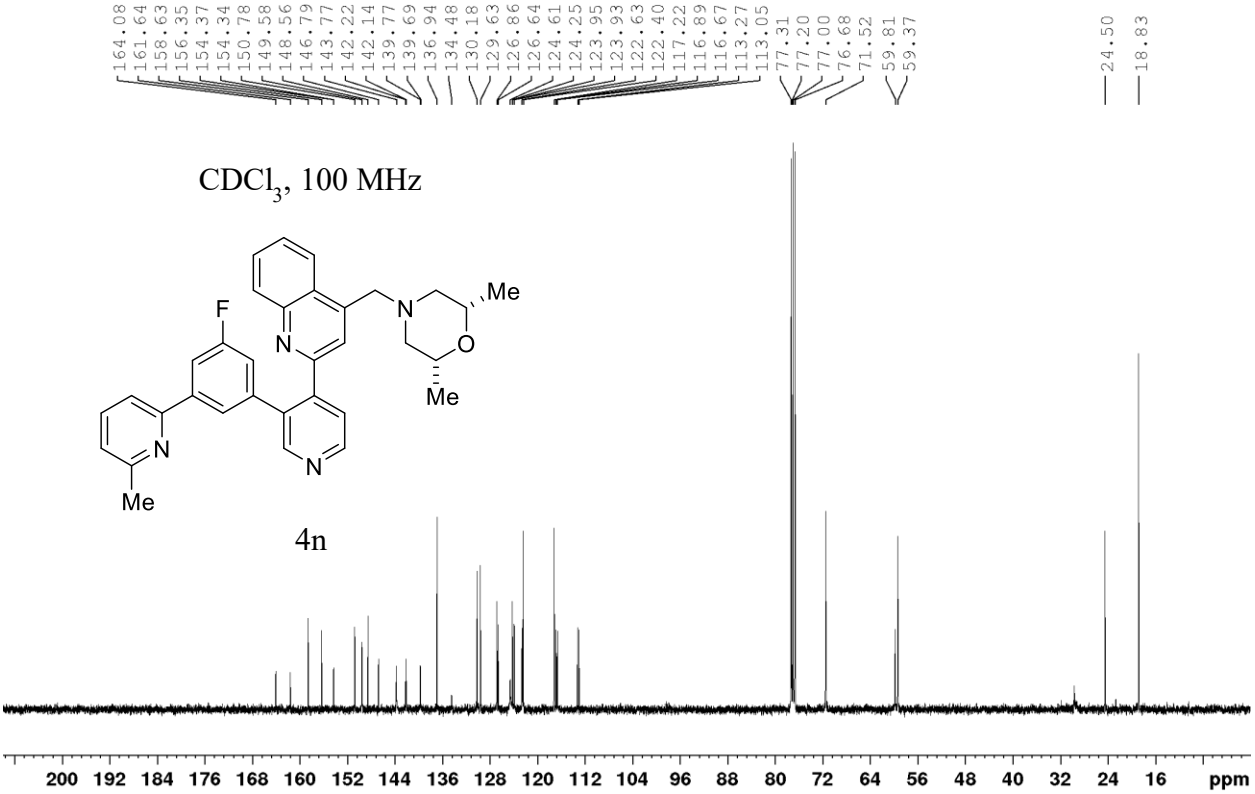


41

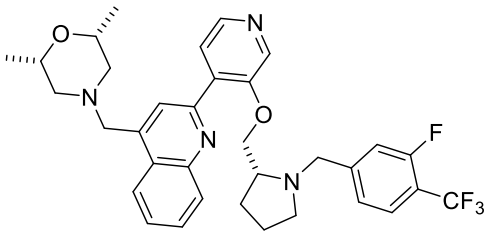

8.75
8.73
8.55
8.53
7.71
7.68
7.68
7.58
7.56
7.54
7.53
7.35
7.34
7.26
7.22
7.20
7.19
7.18
7.17
7.12
7.10
7.09
7.06
6.85
6.83
5.47
4.12
4.10
4.08
4.06
3.59
3.58
3.57
3.56
3.55
3.54
3.44
3.43
3.42
3.12
3.11
3.10
3.09
3.08
3.07
3.06
2.59
1.65
1.64
1.63
1.62
1.60
1.48
1.47
1.46
1.45
1.44
1.25
1.23
1.21
CDCl3, 400 MHz
Me
N
N
F
Cl
N
O
N
CO2Et
4m
1.79
1.00
1.07
2.06
1.00
3.01
4.95
1.02
1.02
2.02
2.02
1.03
1.98
2.97
2.30
2.19
4.33
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


164.19
161.96
161.74
158.65
155.39
154.26
154.23
151.06
149.51
147.17
145.08
142.25
142.17
139.54
138.96
138.88
136.95
134.46
133.31
128.53
127.81
123.97
123.94
122.49
122.46
121.01
117.22
116.66
116.43
113.40
113.18
80.38
77.32
77.20
77.00
76.68
72.19
61.20
40.78
40.72
30.88
30.68
24.62
14.66
CDCl3, 100 MHz
Me
N
N
F
Cl
N
O
N
CO2Et
4m
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
ppm

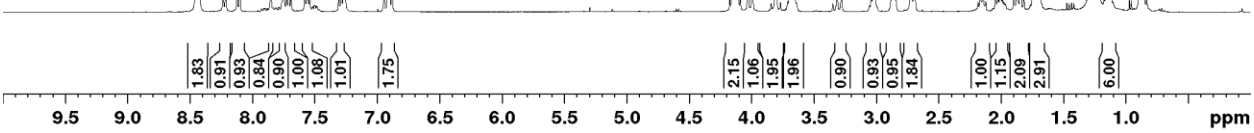

8.79
8.21
8.19
8.19
8.17
7.76
7.74
7.73
7.67
7.56
7.49
7.47
7.24
7.21
7.19
7.08
7.05
7.03
6.88
3.60
3.44
2.47
2.39
2.36
1.63
1.61
1.58
1.22
0.98
0.97
CDCl3, 400 MHz
F
N
N
N
Me
N
O
Me
Me
4n
1.98
2.00
3.01
1.06
1.03
1.03
1.03
1.91
0.99
1.94
1.96
3.05
2.05
2.02
6.22
Chemical Shift (ppm)

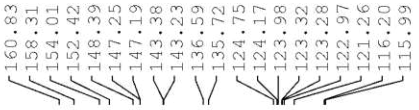

164.08
161.64
158.63
156.35
154.37
154.34
150.78
149.58
148.56
146.79
143.77
142.22
142.14
139.77
139.69
136.94
134.48
130.18
129.63
126.86
126.64
124.61
124.25
123.95
123.93
122.63
122.40
117.22
116.89
116.67
113.27
113.05
77.31
77.20
77.00
76.68
71.52
59.81
59.37
24.50
18.83
CDCl3, 100 MHz
F
N
N
N
Me
N
O
Me
Me
4n
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
ppm

$CDCl_3$, 400 MHz

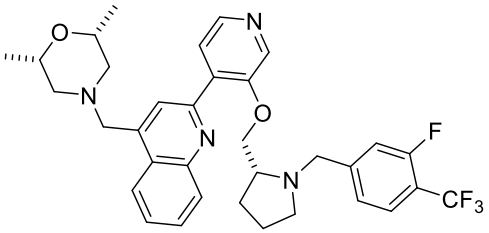


4o

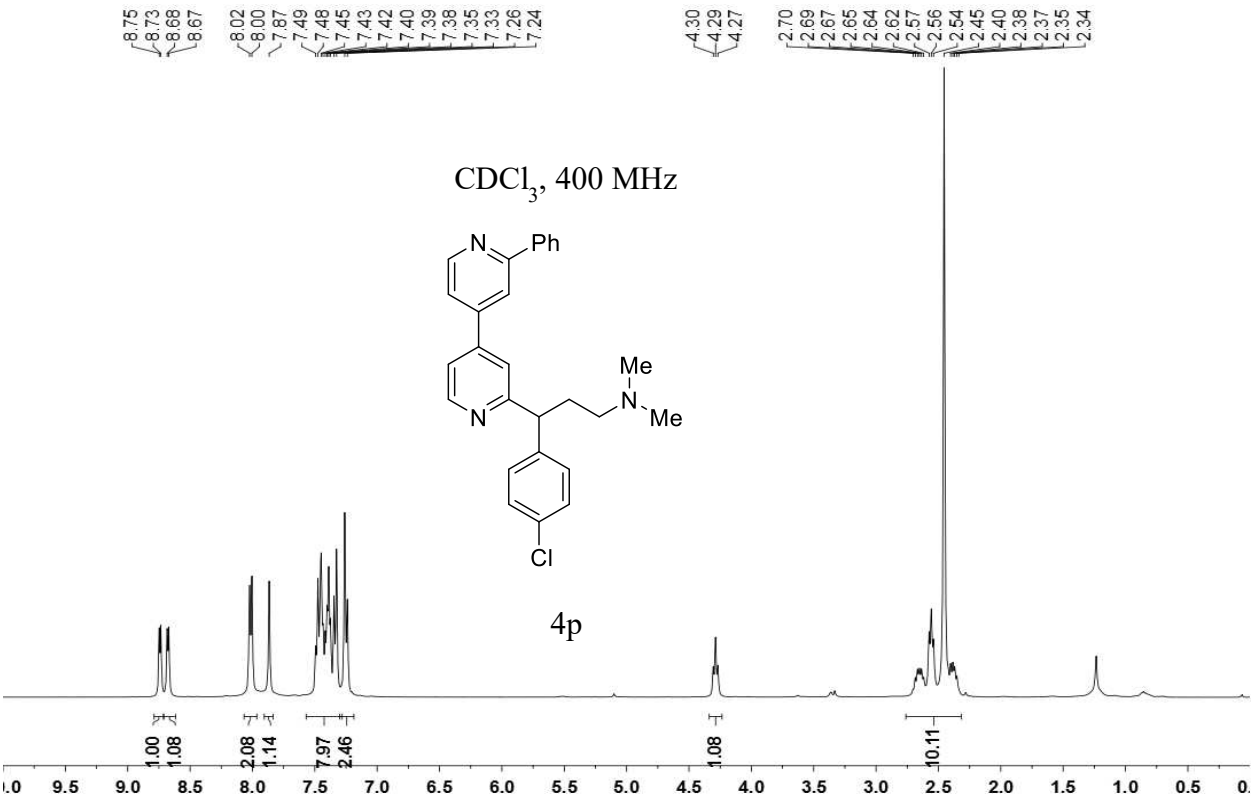


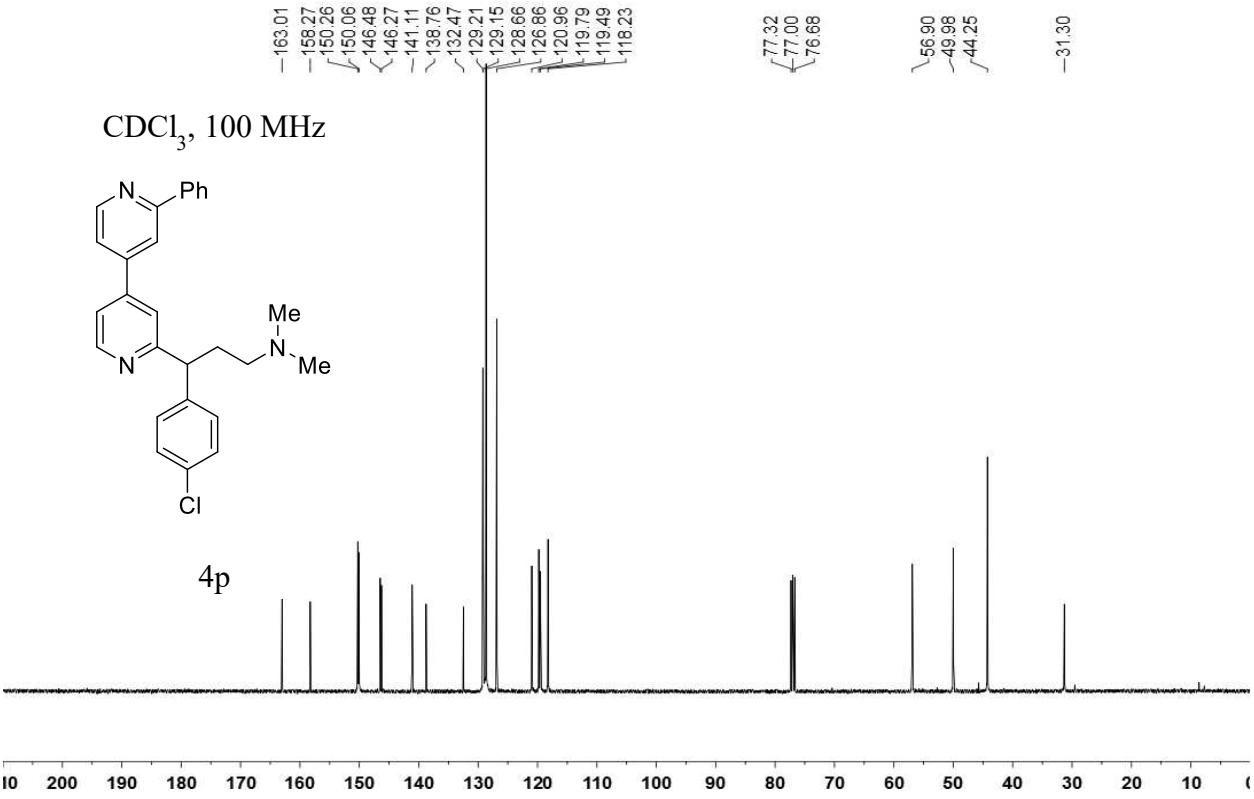


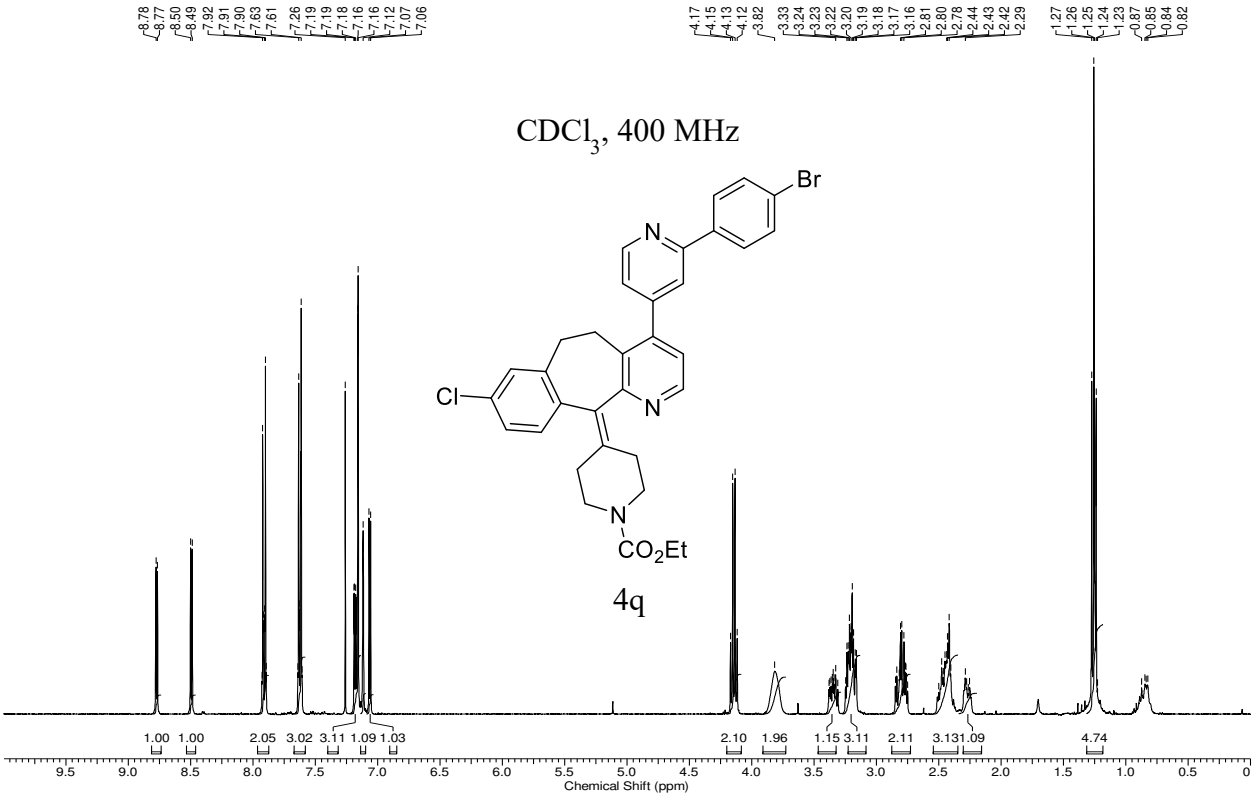
$CDCl_3$, 100 MHz

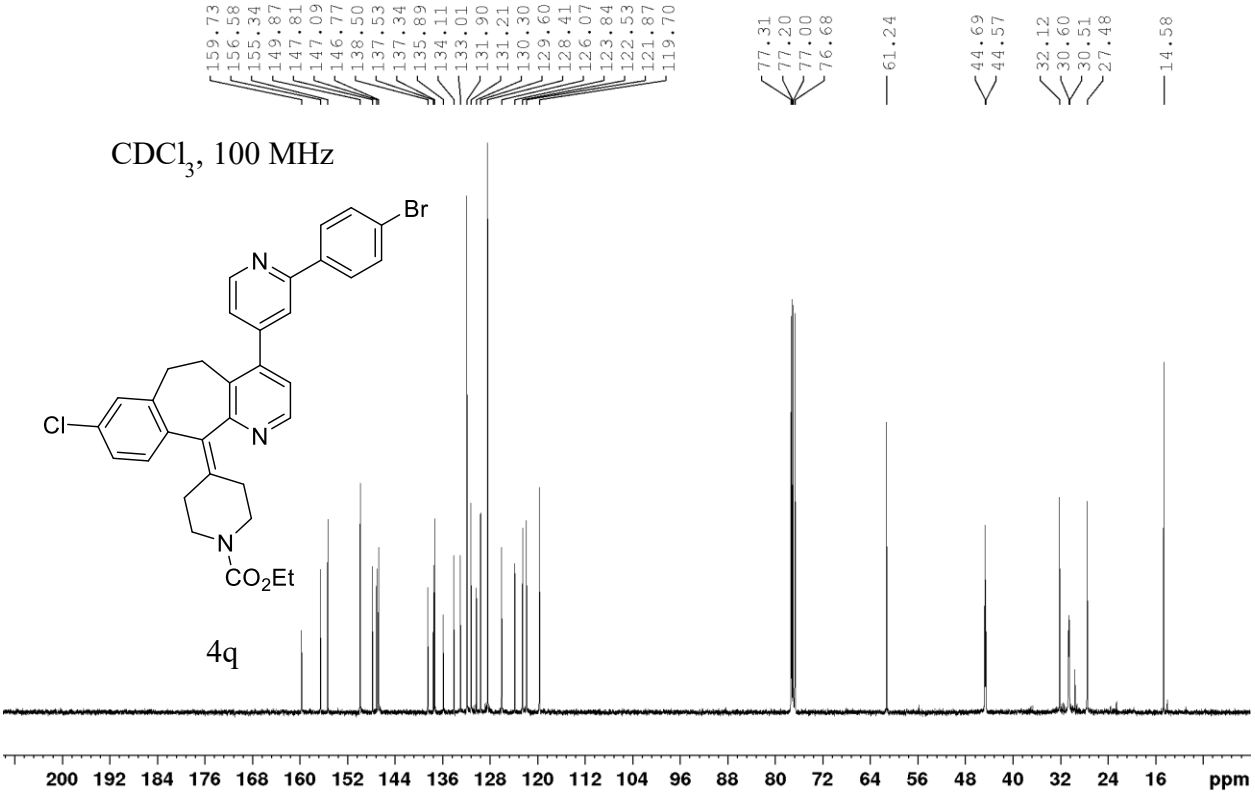


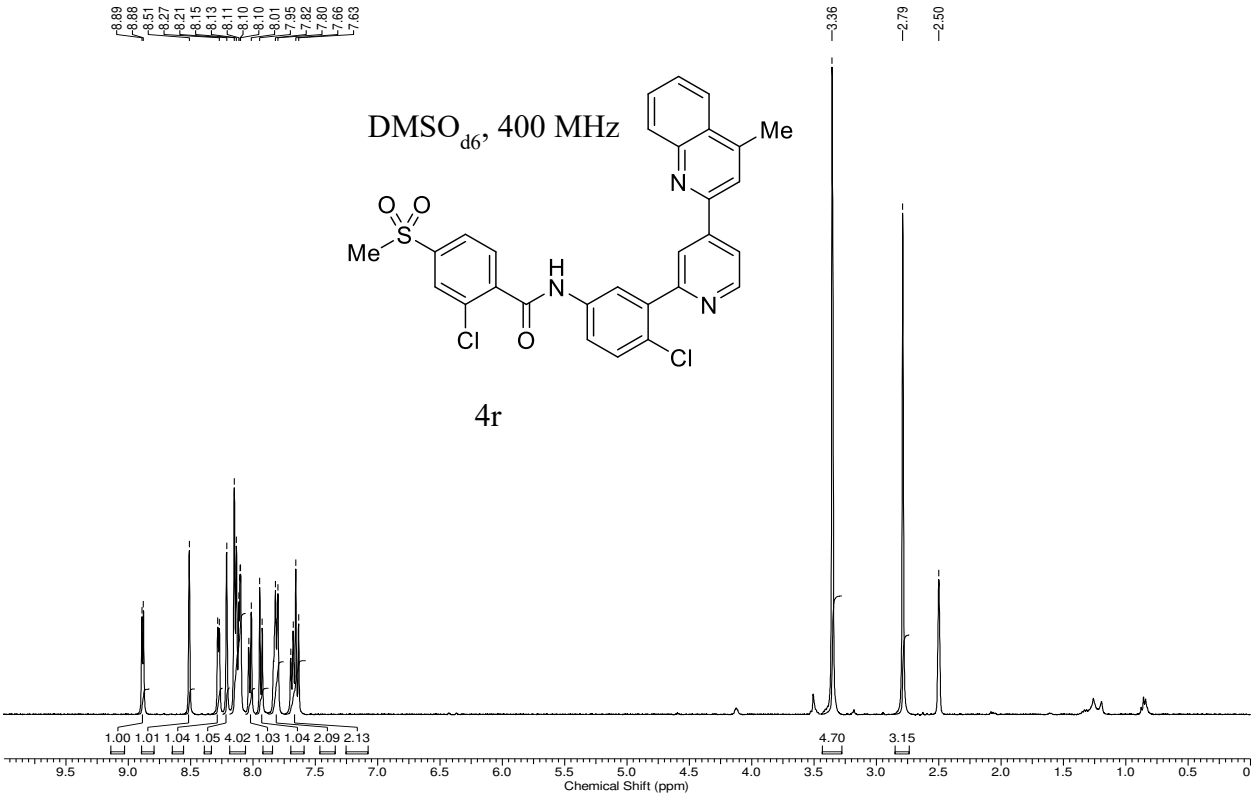
4o


8.75
8.73
8.68
8.67
8.02
8.00
7.87
7.49
7.48
7.45
7.43
7.42
7.40
7.39
7.38
7.35
7.33
7.26
7.24
4.30
4.29
4.27
2.70
2.69
2.67
2.65
2.64
2.62
2.57
2.56
2.54
2.45
2.40
2.38
2.37
2.35
2.34
CDCl3, 400 MHz
N
Ph
N
Me
N
Me
Cl
4p
1.00
1.08
2.08
1.14
7.97
2.46
1.08
10.11

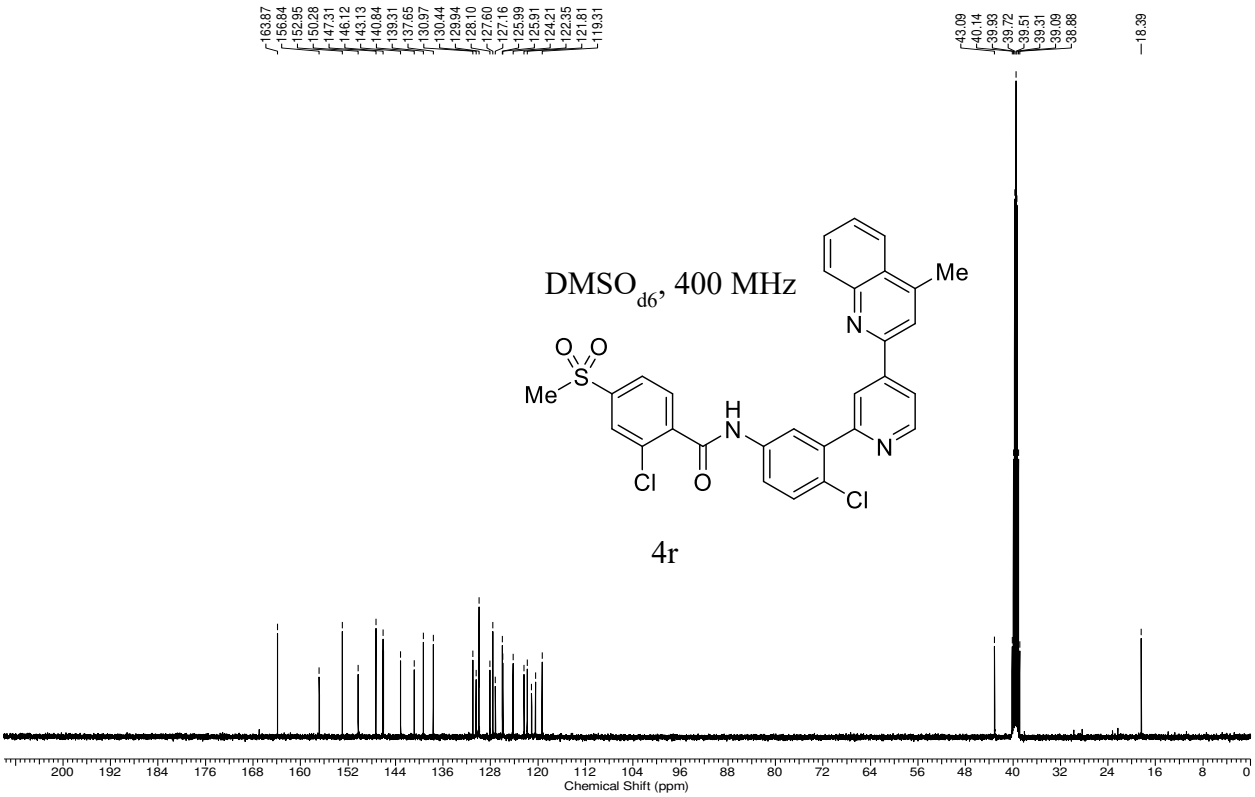

163.01
158.27
150.26
150.06
146.48
146.27
141.11
138.76
132.47
129.21
129.15
128.66
126.86
120.96
119.79
119.49
118.23
77.32
77.00
76.68
56.90
49.98
44.25
31.30
CDCl3, 100 MHz
N
Ph
N
Me
N
Me
Cl
4p


CDCl3, 400 MHz
Br
N
Cl
N
N
CO2Et
4q
Chemical Shift (ppm)

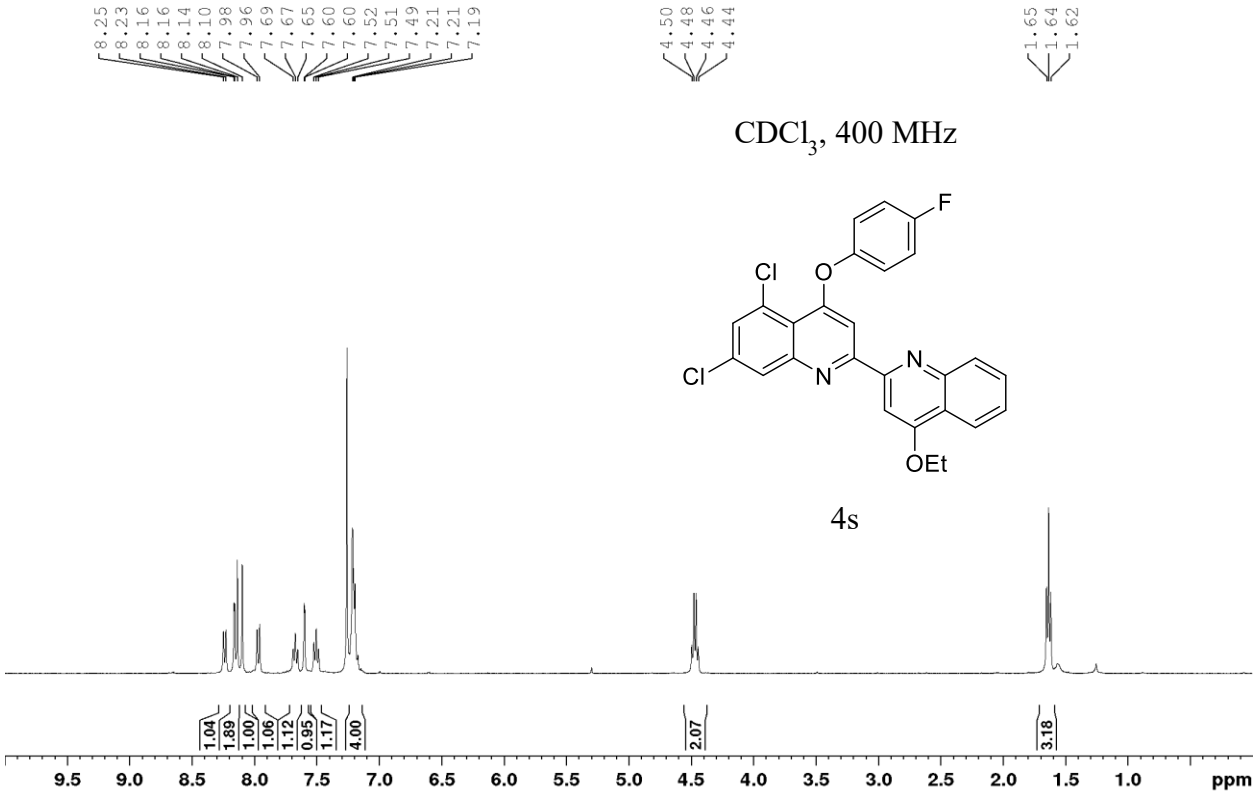

CDCl3, 100 MHz
Br
N
Cl
N
N
CO2Et
4q
ppm

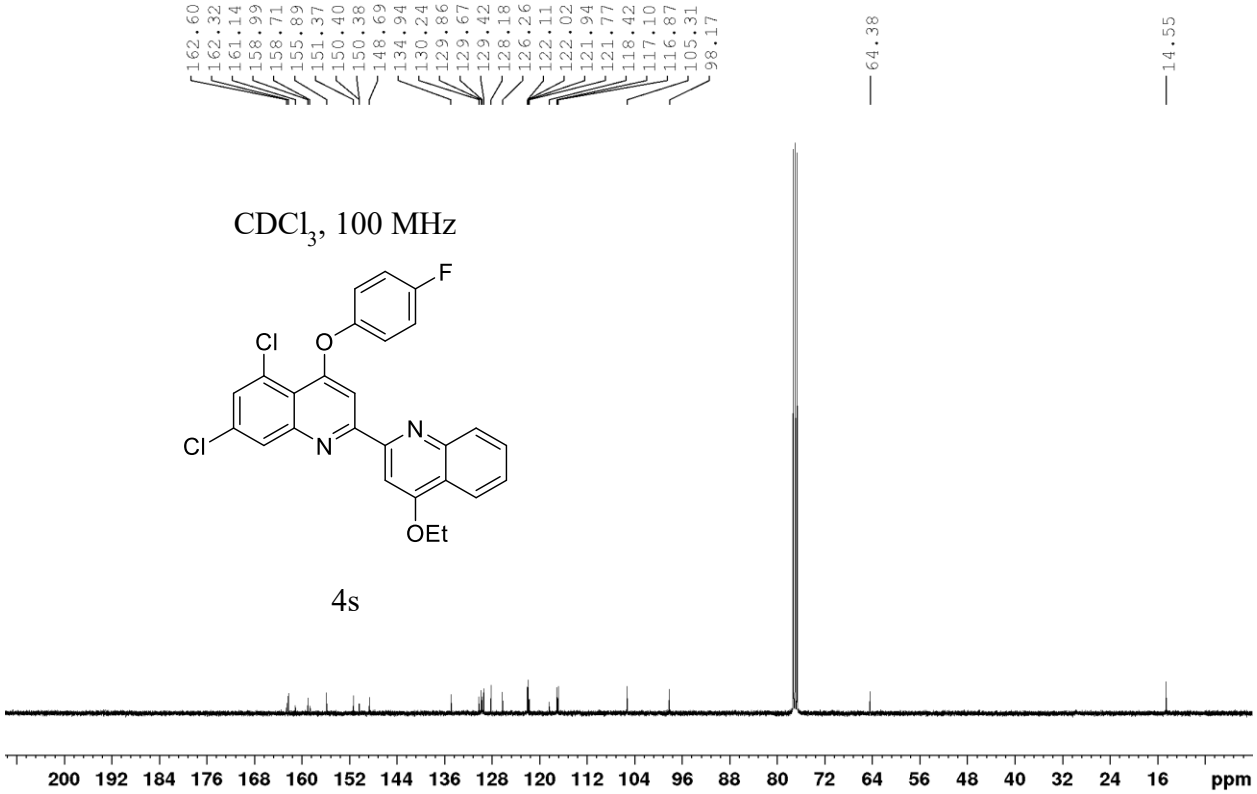

8.89
8.88
8.51
8.27
8.21
8.15
8.13
8.11
8.10
8.10
8.01
7.95
7.82
7.80
7.66
7.63
3.36
2.79
2.50
DMSO$_{d6}$, 400 MHz
Me
N
O
O
S
Me
H
N
N
Cl
O
Cl
1.00 1.01 1.04 1.05 4.02 1.03 1.04 2.09 2.13
4.70
3.15
Chemical Shift (ppm)

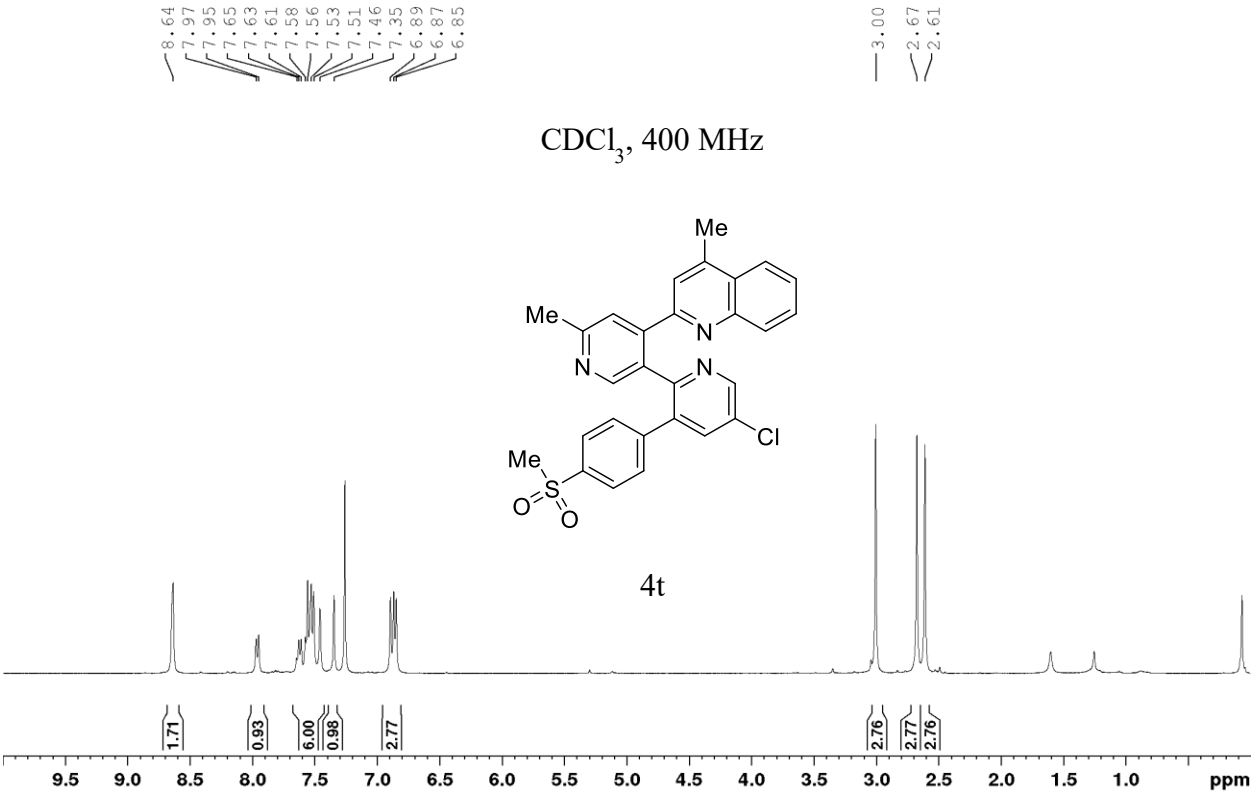
4r


163.87
156.84
152.95
150.28
147.31
146.12
143.13
140.84
139.31
137.65
130.97
130.44
129.94
128.10
127.60
127.16
125.99
125.91
124.21
122.35
121.81
119.31
43.09
40.14
39.93
39.72
39.51
39.31
39.09
38.88
18.39
DMSO$_{d6}$, 400 MHz
Me
N
O
O
S
Me
H
N
N
Cl
O
Cl
Chemical Shift (ppm)

4r

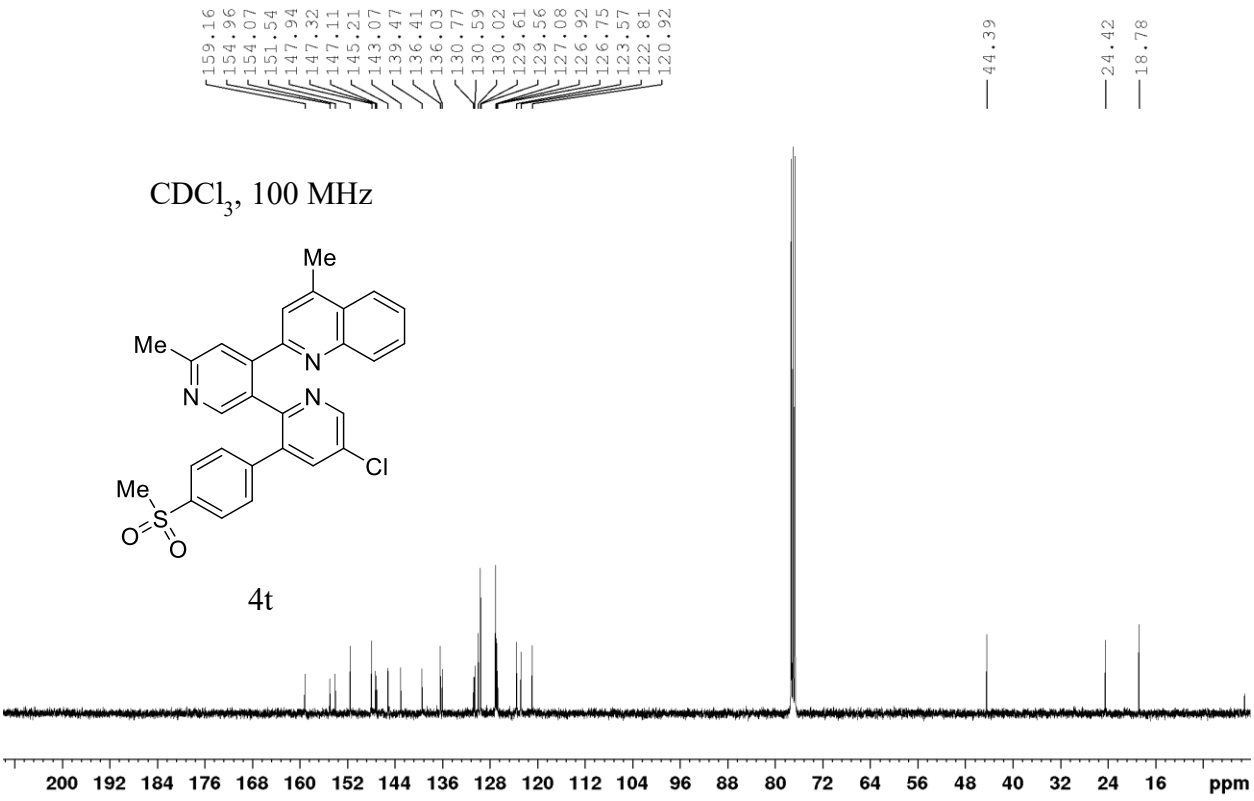

8.25
8.23
8.16
8.16
8.14
8.10
7.98
7.96
7.69
7.67
7.65
7.60
7.60
7.52
7.51
7.49
7.21
7.21
7.19
4.50
4.48
4.46
4.44
1.65
1.64
1.62
CDCl3, 400 MHz
F
Cl
O
Cl
N
N
OEt
4s
1.04
1.89
1.00
1.06
1.12
0.95
1.17
4.00
2.07
3.18
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm


162.60
162.32
161.14
158.99
158.71
155.89
151.37
150.40
150.38
148.69
134.94
130.24
129.86
129.67
129.42
128.18
126.26
122.11
122.02
121.94
121.77
118.42
117.10
116.87
105.31
98.17
64.38
14.55
CDCl3, 100 MHz
F
Cl
O
Cl
N
N
OEt
4s
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16
ppm



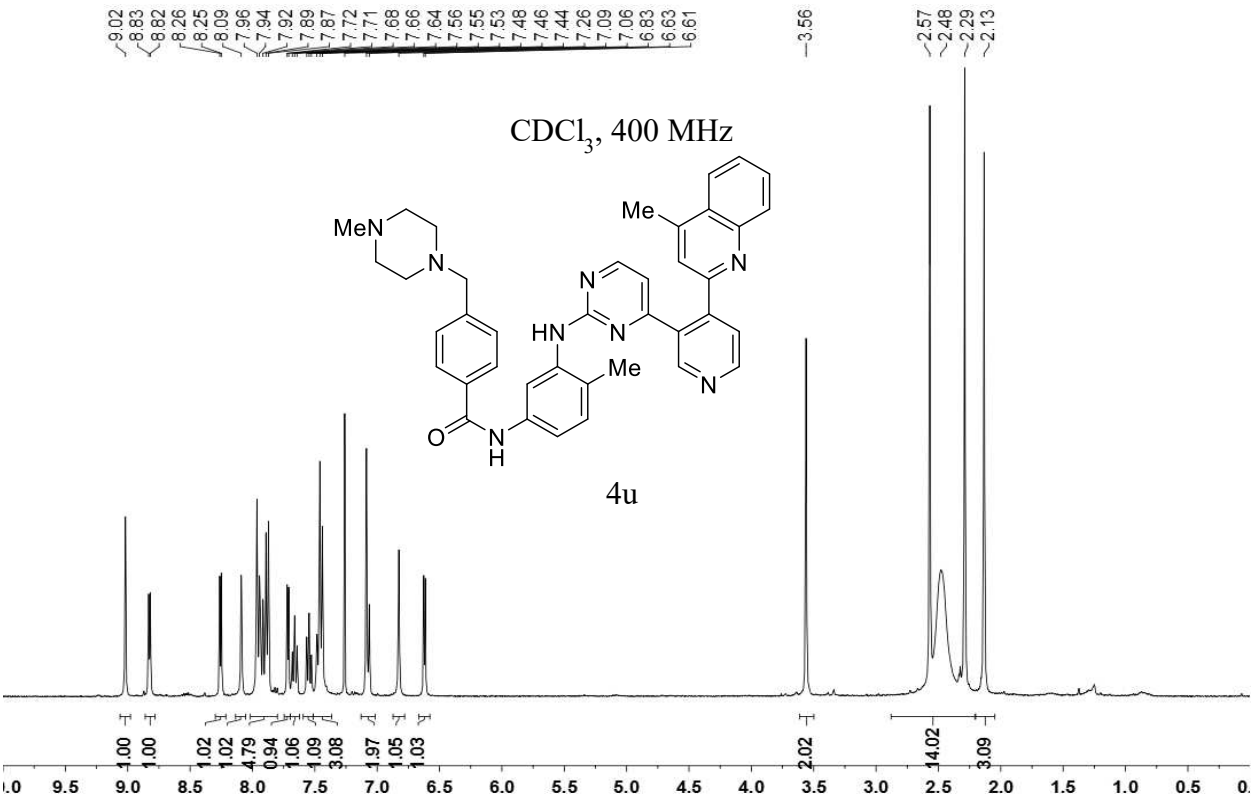
$CDCl_3$, 400 MHz

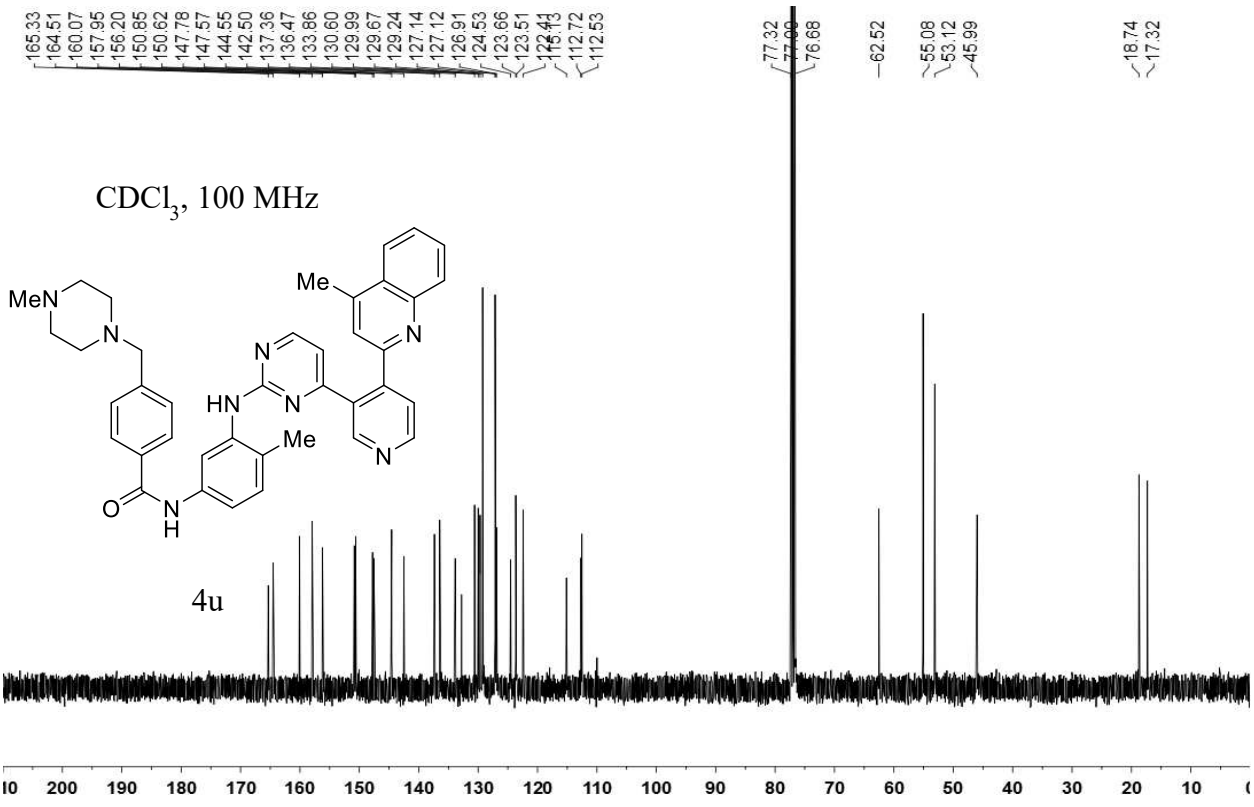
4t



$CDCl_3$, 100 MHz

4t


CDCl3, 400 MHz
4u


CDCl3, 100 MHz
4u

APPENDIX THREE

Bis-Heterobiaryl Formation from Chloroazines: Experimental

(Combined Work of Ben Boyle and Michael Hilton)

A 3.1 General Methods and Materials

$HPPh_2$ (99%) was purchased from Oakwood Chemicals and stored in a glovebox. (2,2,2)-Trifluoroethanol (TFE) was purchased from Oakwood Chemicals and used without further purification. Anhydrous chlorobenzene (>99.8%) was purchased from Sigma Aldrich chemical company and used without further purification. HCl (4.0 M in dioxanes) and trifluoromethanesulfonic acid (98%) were purchased from Sigma Aldrich chemical company and used without further purification but were routinely stored in a –20 ºC fridge. KPF_6 (>99%) was purchased from Sigma Aldrich chemical company and used without further purification but was routinely stored in a desiccator. NaOTf was purchased from Oakwood Chemicals and used without further purification but was routinely stored in a desiccator. All reactions were run under a nitrogen atmosphere unless otherwise noted.

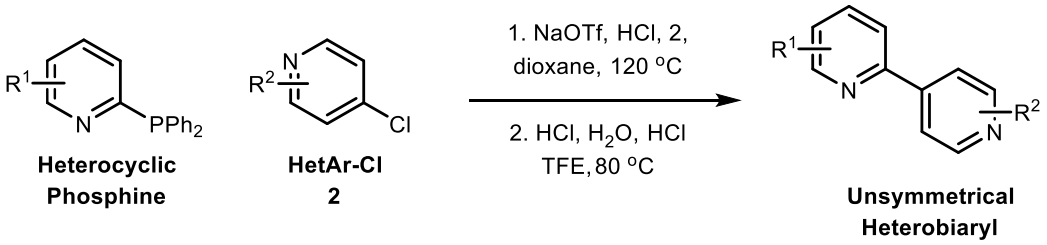
A 3.2 Instrumentation

^{1}H NMR spectra were recorded using a Bruker Ultrashield–400, a Varian 400 MR or an Agilent Inova 400 spectrometer. The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: $CDCl_3$ (7.26 ppm), $(CD_3)_2SO$ (2.50 ppm), or CD_3OD (3.31 ppm). Coupling constants (*J*) were reported in Hertz (Hz) and the multiplicity was reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m

= multiplet, br = broad. ^{13}C NMR spectra were recorded using a Bruker Ultrashield–400, a Varian 400 MR or an Agilent Inova 400 spectrometer. The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: $CDCl_3$ (77.16 ppm), $(CD_3)_2SO$ (39.51 ppm), or CD_3OD (49.00 ppm). Low–resolution mass spectra were recorded on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared spectra were recorded on a Bruker Tensor 27 FT–IR spectrometer with absorptions reported in wavenumbers (cm^{-1}). Melting points were recorded using a Büchi B–450 melting point apparatus.

A 3.3. General Procedures

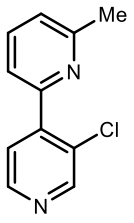
A 3.3.1 General Procedure A (2,4′ or 4,4′-bipyridine synthesis)



An oven dried 8 mL vial with a septa cap was charged with the heterocyclic phosphine (1.0 equiv), sodium trifluoromethanesulfonate (3.2 equiv) and heteroaryl chloride 2 (1.2 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill and then dioxane (2.0M) and 4.0M HCl in dioxane (1.0 equiv) were added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 120 ºC and allowed to stir for the stated time. The reaction was allowed to cool to room temperature before the septa cap was removed and 4.0M HCl in dioxanes (1.0 equiv), H_2O (10 equiv), and TFE (dilute to 0.4M) were quickly added. The reaction vial was heated to 80 ºC and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried

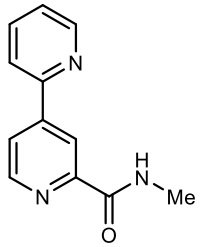
($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl.

3'-Chloro-6-methyl-2,4'-bipyridine (5a)



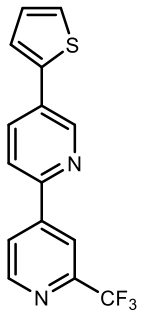
Prepared according to general procedure A using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 3,4-dichloropyridine (44 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and dioxanes (0.13 mL) at 120 °C for 17 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 22 hours. Flash column chromatography (silica gel: 45% EtOAc in hexanes) afforded the title compound as a white crystalline solid (41 mg, 0.20 mmol, 81% yield). mp 59-60 °C; IR ν_{max}/cm^{-1} (film): 3063, 3035, 3014, 3002, 2958, 1371, 1248, 980, 750, 742, 613; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, s), 8.57 (1H, d, *J* = 5.0 Hz), 7.70 (1H, t, *J* = 7.8 Hz), 7.57 (1H, d, *J* = 4.9 Hz), 7.52 (1H, d, *J* = 7.7 Hz), 7.23 (1H, d, *J* = 7.7 Hz), 2.64 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 153.6, 150.4, 148.2, 146.3, 136.6, 129.9, 125.5, 123.3, 121.7, 24.8; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 205.1, $C_{11}H_{10}ClN_2^+$ requires 205.1.

N-methyl-[2,4'-bipyridine]-2'-carboxamide (5b)



Prepared according to general procedure A except with additional 4.0M HCl in dioxanes (1.2 equiv.) using 2-(diphenylphosphaneyl)pyridine (66 mg, 0.25 mmol), 4-chloro-N-methylpicolinamide (51 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (75 μL, 0.3 mmol), and dioxanes (0.13 mL) at 120 °C for 22 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 25.5 hours. Flash column chromatography (silica gel: 70% EtOAc in hexanes) afforded the title compound as a colorless oil (42 mg, 0.20 mmol, 79% yield). IR ν_{max}/cm^{-1} (film): 3404, 3053, 2926, 1670, 1603, 1587, 1533, 1461, 1433, 1412, 1265, 735; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, d, *J* = 4.9 Hz), 8.69 (1H, d, *J* = 1.8 Hz), 8.63 (1H, d, *J* = 5.1 Hz), 8.16 (1H, dd, *J* = 5.1, 1.9 Hz), 8.08 (1H, br s), 7.91 (1H, d, *J* = 7.9 Hz), 7.86–7.77 (1H, m), 7.34 (1H, ddd, *J* = 7.5, 4.8, 1.1 Hz), 3.05 (3H, d, *J* = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.9, 153.9, 150.6, 150.1, 148.8, 147.9, 137.1, 124.1, 123.5, 121.1, 119.2, 26.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 214.1, $C_{12}H_{12}N_3O^+$ requires 214.1.

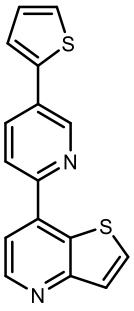
5-(Thiophen-2-yl)-2'-(trifluoromethyl)-2,4'-bipyridine (5c)



Prepared according to general procedure A using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 4-chloro-2-(trifluoromethyl)pyridine (31 μL, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μL, 0.25

mmol), and dioxanes (0.13 mL) at 120 °C for 24 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 22 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a faint yellow crystalline solid (44 mg, 0.14 mmol, 57% yield). mp 93-94 °C; IR ν_{max}/cm^{-1} (film): 3071, 3046, 2954, 2922, 2851, 1606, 1572, 1471, 958, 856, 749; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.03 (1H, dd, *J* = 2.4, 0.9 Hz), 8.84 (1H, d, *J* = 5.1 Hz), 8.37 (1H, dd, *J* = 1.7, 0.8 Hz), 8.12 (1H, dd, *J* = 5.1, 1.7 Hz), 8.03 (1H, dd, *J* = 8.3, 2.4 Hz), 7.88 (1H, dd, *J* = 8.3, 0.9 Hz), 7.51-7.41 (2H, m), 7.18 (1H, dd, *J* = 5.1, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.7, 150.9, 149.4 (d, *J* = 34.54 Hz), 147.8, 147.5, 139.7, 134.1, 131.5, 128.8, 127.2, 125.2, 123.4, 123.3, 121.9 (q, *J* = 274.34 Hz), 117.9 (d, *J* = 2.57 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: −67.99; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 307.1, $C_{15}H_{10}F_3N_2S^+$ requires 307.1.

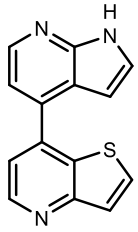
7-(5-(Thiophen-2-yl)pyridin-2-yl)thieno[3,2-b]pyridine (5d)



Prepared according to general procedure A using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 7-chlorothieno[3,2-b]pyridine (51 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and dioxanes (0.13 mL) at 120 °C for 12 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 22 hours. Flash column chromatography

(silica gel: 50% EtOAc in hexanes) afforded the title compound as a bright yellow crystalline solid (55 mg, 0.19 mmol, 75% yield). mp 129-130 °C; IR ν_{max}/cm^{-1} (film): 3089, 3063, 3041, 3004, 2975, 2923, 2852, 2520, 2157, 1555, 1389, 1139, 1026, 832, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15 (1H, dd, *J* = 2.1, 1.1 Hz), 8.83 (1H, d, *J* = 4.9 Hz), 8.12-8.02 (2H, m), 7.90 (1H, d, *J* = 5.7 Hz), 7.76 (1H, d, *J* = 4.9 Hz), 7.64 (1H, d, *J* = 5.7 Hz), 7.50 (1H, dd, *J* = 3.6, 1.1 Hz), 7.43 (1H, dd, *J* = 5.0 Hz), 7.18 (1H, dd, *J* = 5.1, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4, 152.5, 147.5, 146.0, 140.0, 139.9, 134.6, 133.7, 130.5, 129.8, 128.7, 126.8, 124.9, 124.8, 121.2, 115.0; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 295.1, $C_{16}H_{11}N_2S_2^+$ requires 295.0.

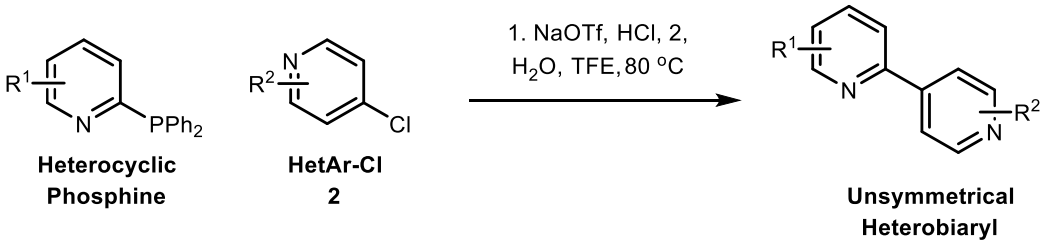
7-(1H-pyrrolo[2,3-b]pyridin-4-yl)thieno[3,2-b]pyridine (5e)



Prepared according to general procedure A using 4-(diphenylphosphaneyl)-1H-pyrrolo[2,3-b]pyridine (76 mg, 0.25 mmol), 7-chlorothieno[3,2-b]pyridine (51 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and dioxanes (0.13 mL) at 120 °C for 18.5 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 24 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as an white crystalline solid (37 mg, 0.15 mmol, 58% yield). mp 250-251 °C; IR ν_{max}/cm^{-1} (film): 3122, 2996, 2924, 2860, 2762, 2710, 2215, 2041, 1557, 1541, 1325; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.79 (1H, s), 8.85 (1H, d, *J* = 4.8 Hz), 8.50 (1H, d, *J* = 5.0 Hz), 7.81 (1H, d, *J* = 5.6 Hz), 7.68 (1H, d, *J* = 5.6 Hz), 7.52 (1H, d, *J* = 4.7 Hz), 7.50-7.42 (2H, m), 6.55 (1H, dd, *J* = 3.6, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$)

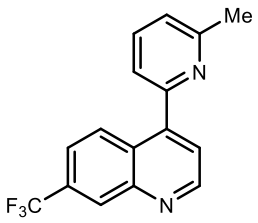
δ: 157.4, 149.5, 147.8, 143.4, 141.8, 138.5, 132.3, 131.3, 126.0, 125.7, 118.8, 118.3, 115.2, 100.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 252.1, $C_{14}H_{10}N_3S^+$ requires 252.1.

A 3.3.2 General Procedure B (Couplings involving quinolines/diazines)



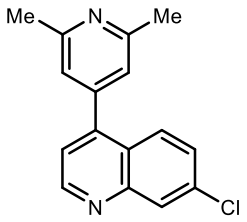
An oven dried 8 mL vial with a septa cap was charged with the heterocyclic phosphine (1.0 equiv), sodium trifluoromethanesulfonate (2.2 equiv) and heteroaryl chloride 2 (1.2 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill and then TFE (0.4M), H_2O (10 equiv), and HCl (1.2 equiv) were added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 80 ºC and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl.

4-(6-Methylpyridin-2-yl)-7-(trifluoromethyl)quinoline (5f)



Prepared according to general procedure B using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 4-chloro-7-(trifluoromethyl)quinoline (69 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 15.5 hours. Flash column chromatography (silica gel: 25% EtOAc in hexanes) afforded the title compound as an white crystalline solid (53 mg, 0.19 mmol, 73% yield). mp 54-55 °C; IR ν_{max}/cm^{-1} (film): 3053, 2954, 2856, 1655, 1637, 1623, 1574, 1555, 1368, 1080, 872, 662; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.09 (1H, d, *J* = 4.4 Hz), 8.48 (1H, dd, *J* = 2.0, 1.0 Hz), 8.32-8.26 (1H, m), 7.80 (1H, t, *J* = 7.7 Hz), 7.71 (1H, dd, *J* = 8.9, 1.9 Hz), 7.62 (1H, d, *J* = 4.4 Hz), 7.42 (1H, d, *J* = 7.6 Hz), 7.31 (1H, d, *J* = 7.8 Hz), 2.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 155.4, 151.5, 148.1, 146.7, 137.3, 131.3 (q, *J* = 32.85 Hz), 128.0-127.7 (2C, m), 127.5, 124.1 (q, *J* = 272.54 Hz), 123.2, 123.1, 122.7-122.5 (m), 121.9, 24.8; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −62.81; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 289.2, $C_{16}H_{12}F_3N_2^+$ requires 289.1.

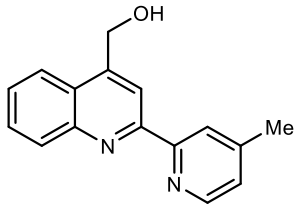
7-Chloro-4-(2,6-dimethylpyridin-4-yl)quinoline (5g)



Prepared according to general procedure B using 4-(diphenylphosphaneyl)-2,6-dimethylpyridine (73 mg, 0.25 mmol), 4,7-dichloroquinoline (60 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 14 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a white crystalline solid (46 mg, 0.17

mmol, 69% yield). mp 88-90 °C; IR ν_{max}/cm^{-1} (film): 3361, 3087, 3040, 3026, 2961, 2857, 1551, 1349, 822, 735, 656, 591; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, s), 8.19 (1H, d, *J* = 2.1 Hz), 7.77 (1H, d, *J* = 9.0 Hz), 7.49 (1H, dd, *J* = 9.0, 2.2 Hz), 7.30 (1H, d, *J* = 4.4 Hz), 7.07 (2H, s), 2.64 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 151.1, 149.2, 146.5, 146.1, 135.8, 129.1, 128.2, 126.9, 124.6, 121.1, 120.8, 24.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 269.1, $C_{16}H_{14}ClN_2^+$ requires 269.1.

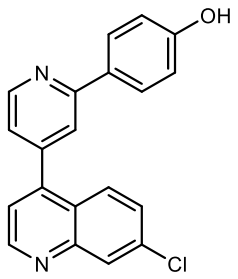
(2-(4-Methylpyridin-2-yl)quinolin-4-yl)methanol (5h)



Prepared according to general procedure B using 2-(diphenylphosphaneyl)-4-methylpyridine (69 mg, 0.25 mmol), (2-chloroquinolin-4-yl)methanol (58 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 ºC for 43 hours. Flash column chromatography (silica gel: 4% MeOH in CH_2Cl_2) followed by a second flash column (silica gel: 3% MeOH in CH_2Cl_2) afforded the title compound as an off-white powder (26 mg, 0.10 mmol, 42% yield). mp 154-157 ºC; IR ν_{max}/cm^{-1} (film): 3292, 2923, 2852, 1602, 1555, 1509, 1480, 1447, 1332, 1093, 1080, 826, 763; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, s), 8.56 (1H, d, *J* = 5.0 Hz), 8.41 (1H, d, *J* = 1.7 Hz), 8.17 (1H, dd, *J* = 8.4, 1.3 Hz), 7.95 (1H, dd, *J* = 8.4, 1.4 Hz), 7.70 (1H, ddd, *J* = 8.4, 6.8, 1.4 Hz), 7.52 (1H, ddd, *J* = 8.2, 6.8, 1.3 Hz), 7.18 (1H, dd, *J* = 5.1, 1.7 Hz), 5.20 (2H, s), 3.14 (1H, br s), 2.48 (3H, s); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 156.2, 156.0, 148.9, 148.4, 147.9, 146.7, 130.4,

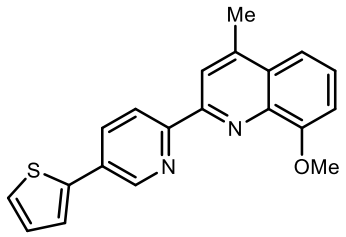
129.4, 126.9, 126.0, 125.2, 123.1, 122.7, 116.7, 62.4, 21.3; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 251.1, $C_{16}H_{15}N_2O^+$ requires 251.1.

4-(4-(7-Chloroquinolin-4-yl)pyridin-2-yl)phenol (5i)



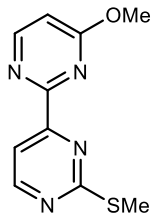
Prepared according to general procedure B using 4-(4-(diphenylphosphaneyl)pyridin-2-yl)phenol (71 mg, 0.20 mmol), 4,7-dichloroquinoline (48 mg, 0.24 mmol), sodium trifluoromethanesulfonate (76 mg, 0.44 mmol), 4.0M HCl in dioxanes (60 μL, 0.24 mmol), H_2O (36 μL, 2.0 mmol), and TFE (0.5 mL) at 80 ºC for 44.5 hours. Flash column chromatography (silica gel: 60% EtOAc in hexanes) afforded the title compound as an off-white powder (50 mg, 0.15 mmol, 75% yield). mp 258-260 ºC; IR ν_{max}/cm^{-1} (film): 3033, 2921, 2850, 1608, 1580, 1539, 1520, 1451, 1419, 1382, 1274, 1240, 1179, 878, 833, 822; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.78 (1H, s), 9.04 (1H, d, *J* = 4.4 Hz), 8.77 (1H, dd, *J* = 4.9, 0.8 Hz), 8.20 (1H, d, *J* = 2.2 Hz), 8.07–8.00 (2H, m), 7.98 (1H, s), 7.89 (1H, d, *J* = 9.0 Hz), 7.71–7.57 (2H, m), 7.42 (1H, dd, *J* = 4.9, 1.5 Hz), 6.87 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 158.8, 156.8, 151.5, 149.7, 148.4, 145.5, 145.4, 134.4, 129.2, 128.3, 128.1, 128.0, 127.3, 124.0, 121.8, 119.4, 115.5; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 333.1, $C_{20}H_{14}ClN_2O^+$ requires 333.1.

8-Methoxy-4-methyl-2-(5-(thiophen-2-yl)pyridin-2-yl)quinoline (5j)



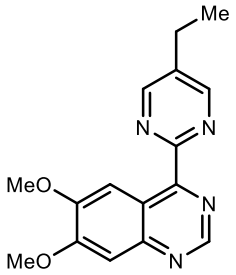
Prepared according to general procedure B using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 2-chloro-8-methoxy-4-methylquinoline (62 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 18 hours. Flash column chromatography (silica gel: 60% EtOAc in Et_2O) followed by a second flash column (silica gel neutralized with NEt_3: gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a yellow amorphous solid (42 mg, 0.13 mmol, 50% yield). IR ν_{max}/cm^{-1} (film): 3070, 2956, 2934, 2832, 1600, 1567, 1546, 1126, 958, 814, 663, 647; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.98 (1H, dd, *J* = 2.4, 0.8 Hz), 8.74 (1H, dd, *J* = 8.3, 0.8 Hz), 8.48 (1H, s), 8.04 (1H, dd, *J* = 8.3, 2.4 Hz), 7.61 (1H, dd, *J* = 8.5, 1.2 Hz), 7.55-7.44 (2H, m), 7.40 (1H, dd, *J* = 5.1, 1.1 Hz), 7.16 (1H, dd, *J* = 5.1, 3.6 Hz), 7.09 (1H, dd, *J* = 7.7. 1.2 Hz), 4.13 (3H, s), 2.80 (3H, d, *J* = 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.1, 155.3, 154.1, 146.1, 145.1, 145.2, 140.6, 139.9, 133.8, 130.6, 129.6, 128.5, 126.8, 126.3, 124.5, 122.2, 120.1, 115.9, 107.9, 56.4, 19.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 333.2, $C_{20}H_{17}N_2OS^+$ requires 333.1.

4-Methoxy-2'-(methylthio)-2,4'-bipyrimidine (5k)



Prepared according to general procedure B using 2-(diphenylphosphaneyl)-4-methoxypyrimidine (74 mg, 0.25 mmol), 4-chloro-2-(methylthio)pyrimidine (35 μL, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 ºC for 13 hours. Flash column chromatography (silica gel, gradient elution: 20% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a white powder (23 mg, 0.10 mmol, 38% yield). mp 93-95 ºC; IR ν_{max}/cm^{-1} (film): 3068, 3035, 2993, 2952, 2923, 2852, 1567, 1553, 1536, 1469, 1370, 1337, 1286, 1207, 843, 788; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, d, *J* = 5.1 Hz), 8.65 (1H, d, *J* = 5.7 Hz), 7.99 (1H, d, *J* = 5.1 Hz), 6.81 (1H, d, *J* = 5.8 Hz), 4.10 (3H, s), 2.66 (3H, s); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 173.8, 170.1, 162.0, 161.8, 158.5, 158.1, 114.9, 109.1, 54.0, 14.4; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 235.1, $C_{10}H_{11}N_4OS^+$ requires 235.1.

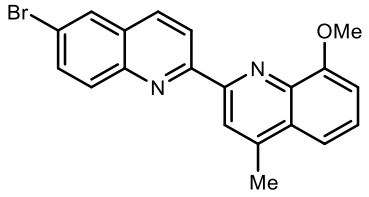
4-(5-Ethylpyrimidin-2-yl)-6,7-dimethoxyquinazoline (5l)



Prepared according to general procedure B using 2-(diphenylphosphaneyl)-5-ethylpyrimidine (73 mg, 0.25 mmol), 4-chloro-6,7-dimethoxyquinazoline (67 mg, 0.30 mmol), sodium

trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 12 hours. Flash column chromatography (silica gel: 4% MeOH in CH_2Cl_2) afforded the title compound as a yellow crystalline solid (40 mg, 0.14 mmol, 54% yield). mp 163-164 °C; IR ν_{max}/cm^{-1} (film): 3090, 3043, 3009, 2928, 1557, 1341, 940, 827, 630, 599, 562; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.34 (1H, s), 8.89 (2H, s), 8.21 (1H, s), 7.42 (1H, s), 4.09 (3H, s), 4.01 (3H, s), 2.82 (2H, q, *J* = 7.6 Hz), 1.40 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.2, 159.0, 157.1 (2C), 156.1, 153.7, 151.0, 151.0, 137.6, 119.1, 107.1, 104.4, 56.6, 56.3, 23.8, 14.9,; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 297.2, $C_{16}H_{17}N_4O_2^+$ requires 297.1.

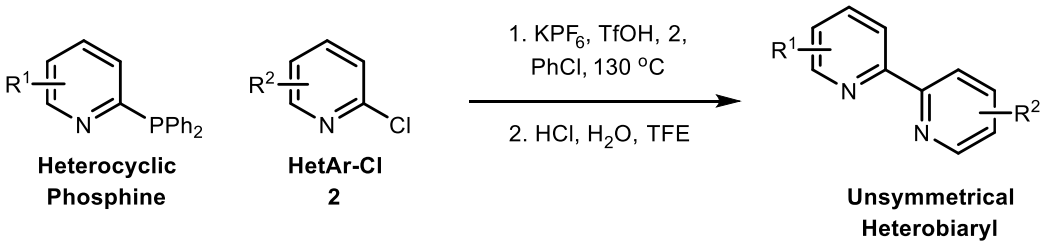
6'-Bromo-8-methoxy-4-methyl-2,2'-biquinoline (5m)



Prepared according to general procedure B using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 2-chloro-8-methoxy-4-methylquinoline (62 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 18 hours. Flash column chromatography (silica gel: 60% EtOAc in hexanes) followed by a second flash column (silica gel: gradient elution: CH_2Cl_2 to 2% MeOH in CH_2Cl_2) afforded the title compound as an orange crystalline solid (60 mg, 0.16 mmol, 63% yield). mp 173-174 °C; IR ν_{max}/cm^{-1} (film): 3496, 3061, 3010, 2969, 2941, 2835, 1592, 1560, 1546, 1402, 1318, 1160, 884; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.92 (1H, dd, *J* = 8.6, 1.9 Hz), 8.70 (1H, s), 8.22 (1H, dd, *J* = 8.7, 1.8 Hz), 8.10 (1H, d, *J* = 8.9 Hz), 8.04 (1H, d, *J* =

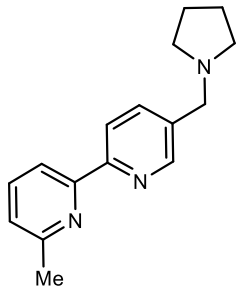
2.1 Hz), 7.81 (1H, dt. *J* = 9.1, 2.1 Hz), 7.63 (1H, d, *J* = 8.4 Hz), 7.54 (1H, dt, *J* = 8.0, 1.9 Hz), 7.12 (1H, d, *J* = 7.7 Hz), 4.15 (3H, d, *J* = 1.9 Hz), 2.84 (3H, d, *J* = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.0, 156.2, 154.1, 146.6, 145.3, 139.9, 135.7, 133.0, 131.6, 129.9, 129.8, 129.6, 127.2, 120.8, 120.8, 120.4, 115.9, 108.0, 56.4, 19.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 379.1, $C_{20}H_{16}BrN_2O^+$ requires 379.0.

A 3.3.3 General Procedure C (2,2′-bipyridines synthesis)



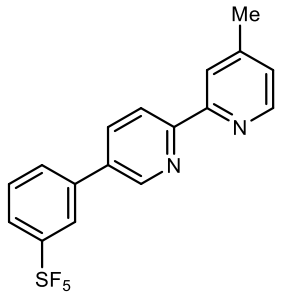
An oven dried 8 mL vial with a septa cap was charged with the heterocyclic phosphine (1.0 equiv), potassium hexafluorophosphate (1.0 equiv), and heteroaryl chloride 2 (2.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill and then chlorobenzene (2.0M) and trifluoromethanesulfonic acid (1.2 equiv) were added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 130 ºC for the stated time. The reaction was then allowed to cool to room temperature. The septa cap was removed and 4.0M HCl in dioxanes (1.0 equiv), H_2O (10 equiv), and TFE (dilute to 0.4M) were quickly added. The reaction vial was then heated at 80 ºC for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl.

6'-Methyl-5-(pyrrolidin-1-ylmethyl)-2,2'-bipyridine (5n)



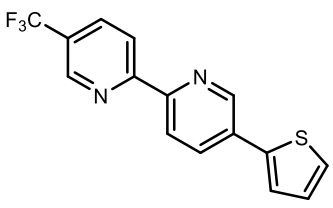
Prepared according to general procedure C using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 2-chloro-5-(pyrrolidin-1-ylmethyl)pyridine (98 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (71 μL, 0.80 mmol), and chlorobenzene (0.13 mL) at 130 ºC for 39.5 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 ºC for 24 hours. Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then gradient elution: 30% EtOAc in hexanes to 70% EtOAc in hexanes) afforded the title compound as an orange oil (22 mg, 0.09 mmol, 35% yield). IR ν_{max}/cm^{-1} (film): 3057, 2960, 2786, 1593, 1573, 1560, 1454 1410, 1347, 1080, 1025, 800, 759; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, *J* = 1.7 Hz), 8.35 (1H, d, *J* = 8.1 Hz), 8.14 (1H, d, *J* = 7.8 Hz), 7.81 (1H, dd, *J* = 8.1, 2.1 Hz), 7.68 (1H, t, *J* = 7.7 Hz), 7.15 (1H, d, J = 7.6 Hz), 3.69 (2H, s), 2.62 (3H, s), 2.58-2.50 (4H, m), 1.83-1.77 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.1, 155.7, 155.6, 149.7, 137.6, 137.2, 134.5, 123.2, 121.0, 118.2, 57.7, 54.2, 24.8, 23.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 254.2, $C_{16}H_{20}N_3^+$ requires 254.2.

4-Methyl-5'-(3-(pentafluoro-λ^6-sulfaneyl)phenyl)-2,2'-bipyridine (5o)



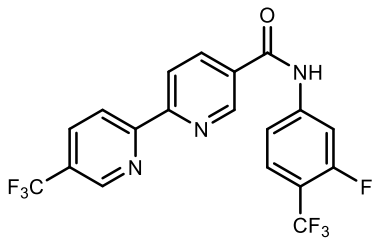
Prepared according to general procedure C using 2-(diphenylphosphaneyl)-4-methylpyridine (69 mg, 0.25 mmol), 2-chloro-5-(3-(pentafluoro-λ^6-sulfaneyl)phenyl)pyridine (158 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 ºC for 39 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 ºC for 22 hours. Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a light tan powder (48 mg, 0.13 mmol, 51% yield). mp 129-131 ºC; IR ν_{max}/cm^{-1} (film): 3022, 2923, 2852, 1606, 1595, 1465, 1435, 1368, 1115, 859, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.89 (1H, s), 8.66-8.44 (2H, m), 8.29 (1H, s), 8.11-7.93 (2H, m), 7.89-7.72 (2H, m), 7.60 (1H, t, *J* = 7.8 Hz), 7.17 (1H, d, *J* = 3.6 Hz), 2.46 (3H, s); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 156.2, 155.3, 154.9 (app t, *J* = 17.4 Hz), 149.2, 148.5, 147.7, 139.0, 135.6, 134.8, 130.3, 129.7, 125.6 (app qn, *J* = 4.5 Hz), 125.2, 124.8 (app qn, *J* = 4.5 Hz), 122.2, 121.4, 21.4; ^{19}F NMR (365 MHz, $CDCl_3$) δ: 83.77 (qn, *J* = 151.8 Hz), 62.75 (d, *J* = 150.0 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 373.2, $C_{17}H_{14}F_5N_2S^+$ requires 373.1.

5-(Thiophen-2-yl)-5'-(trifluoromethyl)-2,2'-bipyridine (5p)



Prepared according to general procedure C using 2-(diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (83 mg, 0.25 mmol), 2-chloro-5-(thiophen-2-yl)pyridine (98 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 °C for 45 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 19 hours. Flash column chromatography (silica gel: 2% EtOAc in hexanes) afforded the title compound as a white crystalline solid (41 mg, 0.13 mmol, 53% yield). IR ν_{max}/cm^{-1} (film): 3124, 3067, 2921, 1599, 1579, 1548, 1530, 1468, 1209, 782, 751, 644; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.98 (1H, dd, *J* = 2.4, 0.8 Hz), 8.93 (1H, dt, *J* = 2.5, 0.9 Hz), 8.58 (1H, dt, *J* = 8.4, 0.8 Hz), 8.49 (1H, dd, *J* = 8.3, 0.8 Hz), 8.09-7.99 (2H, m), 7.47 (1H, dd, *J* = 3.6, 1.1 Hz), 7.42 (1H, dd, *J* = 5.1, 1.1 Hz), 7.17 (1H, dd, *J* = 5.1, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.9, 153.4, 146.6, 146.3 (q, *J* = 4.1 Hz), 140.2, 134.2, (q, *J* = 3.5 Hz), 134.0, 131.4, 128.6, 126.8, 126.4 (q, *J* = 33.00 Hz), 124.9, 123.9 (q, *J* = 272.1 Hz), 121.9, 120.7; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.32; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 307.1, $C_{15}H_{10}F_3N_2S^+$ requires 307.1.

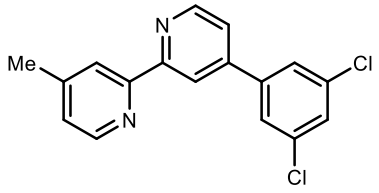
N-(3-fluoro-4-(trifluoromethyl)phenyl)-5'-(trifluoromethyl)-[2,2'-bipyridine]-5-carboxamide (5q)



Prepared according to general procedure C using 2-(diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (66 mg, 0.20 mmol), 6-chloro-N-(3-fluoro-4-(trifluoromethyl)phenyl)nicotinamide (128 mg, 0.40 mmol), potassium hexafluorophosphate (36

mg, 0.20 mmol), trifluoromethanesulfonic acid (21 μL, 0.24 mmol), and chlorobenzene (0.13 mL) at 130 °C for 45 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 19 hours. Preparatory thin layer chromatography (40% EtOAc in hexanes) followed by flash column chromatography (silica gel: 1% MeOH in CH_2Cl_2) afforded the title compound as a white amorphous solid (40 mg, 0.09 mmol, 47% yield). IR ν_{max}/cm^{-1} (film): 3853, 3750, 2923, 2852, 2359, 2342, 1733, 1652, 1598, 1540, 1468, 1426, 1132, 1083, 820, 552, 532; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.06 (1H, s), 9.27 (1H, d, *J* = 2.2 Hz), 9.15 (1H, s), 8.67 (1H, d, *J* = 8.4 Hz), 8.61 (1H, d, *J* = 8.3 Hz), 8.54 (1H, dd, *J* = 8.3, 2.2 Hz), 8.43 (1H, dd, *J* = 8.5, 2.4 Hz), 8.02 (1H, dd, *J* = 13.6, 1.9 Hz), 7.86-7.74 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.4, 160.3, 157.8, 156.2, 149.1, 146.4 (d, *J* = 4.1 Hz), 144.6 (d, *J* = 11.9 Hz), 137.3, 135.2 (d, *J* = 3.7 Hz), 130.7, 127.9 (2C, m), 125.7 (d, *J* = 32.5 Hz), 123.7 (q, *J* = 272.3 Hz), 122.8 (q, *J* = 270.59 Hz), 121.1 (d, *J* = 41.7 Hz), 115.8 (d, *J* = 3.0 Hz), 110.9 (d, *J* = 32.8 Hz), 107.7 (d, *J* = 25.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: −59.19 (d, *J* = 12.0 Hz), −60.89, −114.19 (tt, *J* = 13.0, 6.7 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 430.2, $C_{19}H_{11}F_7N_3O^+$ requires 430.1.

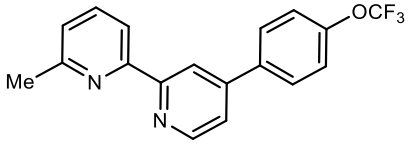
4-(3,5-Dichlorophenyl)-4'-methyl-2,2'-bipyridine (5r)



Prepared according to general procedure C using 2-(diphenylphosphaneyl)-4-methylpyridine (69 mg, 0.25 mmol), 2-chloro-4-(3,5-dichlorophenyl)pyridine (129 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 °C for 43 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in

dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 20 hours. Flash column chromatography (silica gel: 2% MeOH in Et_2O) followed by a second flash column (silica gel: 2% MeOH in CH_2Cl_2) afforded the title compound as a white amorphous solid (46 mg, 0.15 mmol, 58% yield). IR ν_{max}/cm^{-1} (film): 3054, 3011, 2922, 2855, 1670, 1595, 1556, 1490, 1138, 849, 720, 650, 533; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, dd, *J* = 5.0, 0.8 Hz), 8.53 (1H, dd, *J* = 4.9, 0.8 Hz), 8.44 (1H, dd, *J* = 1.7, 0.8 Hz), 8.28 (1H, dt, *J* = 1.6, 0.8 Hz), 7.52 (1H, dd, *J* = 1.8, 0.7 Hz), 7.42-7.32 (3H, m), 7.15 (1H, ddd, *J* = 5.0, 1.7, 0.8 Hz), 2.45 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.7, 155.7, 149.2, 149.1, 148.4, 147.2, 136.8, 135.2, 133.1, 131.9, 130.1, 127.6, 125.1, 124.2, 122.2 121.8, 21.4; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 315.1, $C_{17}H_{13}Cl_2N_2^+$ requires 315.0.

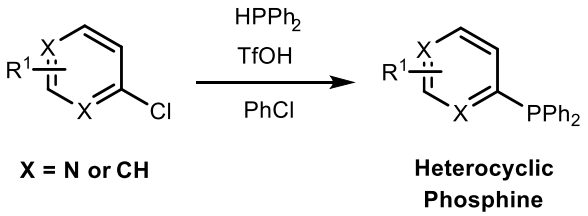
6'-Methyl-4-(4-(trifluoromethoxy)phenyl)-2,2'-bipyridine (5s)



Prepared according to general procedure C using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 2-chloro-4-(4-(trifluoromethoxy)phenyl)pyridine (137 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 °C for 39.5 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 27 hours. Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3: 10% EtOAc in hexanes) afforded the title compound as colorless crystals (47 mg, 0.14 mmol, 57% yield). mp 46-48 °C; IR ν_{max}/cm^{-1} (film): 3055, 3012, 2920, 1587, 1511, 1459, 1271, 1208, 1150, 1106, 1086, 834, 803; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, dd, *J* = 5.1, 0.8 Hz), 8.67-8.62 (1H, m), 8.23

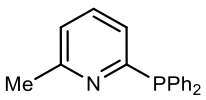
(1H, d, *J* = 7.8 Hz), 7.84-7.75 (2H, m), 7.73 (1H, t, J = 7.7), 7.48 (1H, dd, *J* = 5.1, 1.9 Hz), 7.36 (2H, dq, *J* = 8.6, 1.0 Hz), 7.20 (1H, d, *J* = 7.6 Hz), 2.66 (3H, s); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 158.2, 157.4, 155.5, 150.0 (q, *J* = 1.9 Hz), 149.9, 148.0, 137.4, 137.3, 128.8, 124.5, 121.5, 121.4, 120.6 (q, *J* = 257.7 Hz), 119.2, 118.4, 24.8; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –57.76; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 331.2, $C_{18}H_{14}F_3N_2O^+$ requires 331.1.

A 3.3.4 General Procedure A' (Heterocyclic Phosphine Synthesis: Pyridines)



An oven dried 8 mL vial equipped with a stir bar was charged with the heterocycle (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, chlorobenzene (2.0 M) was added, followed by diphenylphosphine (1.2 equiv), and trifluoromethanesulfonic acid (1.0 equiv). The reaction was heated to 130 ºC and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl phosphine product.

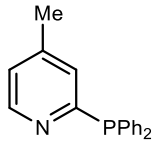
2-(Diphenylphosphaneyl)-6-methylpyridine (6a)



Prepared according to general procedure A' using 2-chloro-6-methylpyridine (0.22 mL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL, 2.00

mmol), and chlorobenzene (1.0 mL) at 130 ºC for 21 hours. Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white powder (522 mg, 1.88 mmol, 94% yield). mp 80-82 ºC; IR ν_{max}/cm^{-1} (film): 3048, 3001, 2961, 1576, 1555, 1443, 1433, 1094, 796, 754, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (1H, td, *J* = 7.2, 1.2 Hz), 7.40-7.29 (10H, m), 7.03 (1H, d, *J* = 7.8 Hz), 6.82 (1H, d, *J* = 7.6 Hz), 2.57 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2 (d, *J* = 7.3 Hz), 159.1 (d, *J* = 14.5 Hz), 136.7 (d, *J* = 11.2 Hz), 136.0, 134.2 (d, *J* = 19.5 Hz), 129.0, 128.6 (d, *J* = 7.1 Hz), 125.0 (d, *J* = 11.6 Hz), 122.1, 24.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –4.96; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 278.1, $C_{18}H_{17}NP^+$ requires 278.1.

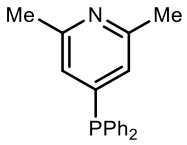
2-(Diphenylphosphaneyl)-4-methylpyridine (6b)



Prepared according to general procedure A' using 2-chloro-4-methylpyridine (0.22 mL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 ºC for 14 hours. Flash column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 15% EtOAc in hexanes) afforded the title compound as a white powder (523 mg, 1.89 mmol, 94% yield). mp 69-71 ºC; IR ν_{max}/cm^{-1} (film): 3066, 3045, 2922, 1584, 1547, 1477, 1457, 1434, 1388, 1373, 1311, 1089, 1025, 999, 826, 752 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (1H, d, *J* = 4.6 Hz), 7.44-7.29 (10H, m), 7.00 (1H, d, *J* = 4.1 Hz), 6.93 (1H, s), 2.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4 (d, *J* = 4.6 Hz), 150.2 (d, *J* = 13.0 Hz), 146.9 (d, *J* = 2.6 Hz), 136.4 (d, *J* = 10.8 Hz), 134.2 (d, *J* = 19.8 Hz), 129.1, 128.9 (d,

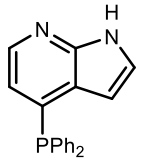
J = 16.4 Hz), 128.7 (d, J = 6.9 Hz), 123.4, 21.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –4.06; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 278.2, $C_{18}H_{17}NP^+$ requires 278.1.

4-(Diphenylphosphaneyl)-2,6-dimethylpyridine (6c)



Prepared according to general procedure A' using 4-chloro-2,6-dimethylpyridine (283 mL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 °C for 20 hours. Flash column chromatography (silica gel: 25% EtOAc in hexanes) afforded the title compound as a white crystalline solid (582 mg, 2.00 mmol, 99% yield). mp 118-119 °C; IR ν_{max}/cm^{-1} (film): 3069, 3052, 3000, 2984, 2954, 2916, 2361, 1739, 1675, 1158, 831, 618, 542; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47-7.29 (10H, m), 6.79 (2H, d, J = 7.2 Hz), 2.46 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5 (d, J = 5.1 Hz),149.0 (d, J = 16.2 Hz), 135.4 (d, J = 10.0 Hz), 134.3 (d, J = 20.3 Hz), 129.5, 128.9 (d, J = 7.5 Hz), 123.9 (d, J = 15.9 Hz), 24.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –6.96; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 292.2, $C_{19}H_{19}NP^+$ requires 292.1.

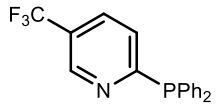
4-(Diphenylphosphaneyl)-1H-pyrrolo[2,3-b]pyridine (6d)



Prepared according to general procedure A' using 4-chloro-1H-pyrrolo[2,3-b]pyridine (305 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol, trifluoromethanesulfonic acid (177

μL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 °C for 20 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a faint yellow crystalline solid (550 mg, 1.82 mmol, 91% yield). mp 146-148 °C; IR ν_{max}/cm^{-1} (film): 3119, 3069, 3054, 2902, 2802, 2763, 1592, 1182, 792, 611; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.76 (1H, s), 8.20 (1H, d, *J* = 4.9 Hz), 7.46-7.31 (11H, m), 6.71-6.57 (1H, m), 6.28 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.6 (d, *J* = 6.9 Hz), 142.2, 140.5 (d, *J* = 17.2 Hz), 135.2 (d, *J* = 20.3 Hz), 134.4 (d, *J* = 20.3 Hz), 129.4, 128.8 (d, *J* = 7.7 Hz), 125.4, 123.3, 119.2 (d, *J* = 4.4 Hz), 101.2 (d, *J* = 6.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: −12.55; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 303.1, $C_{19}H_{16}N_2P^+$ requires 303.1.

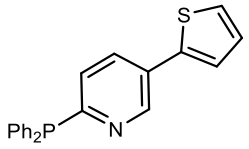
2-(Diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (6e)



Prepared according to general procedure A' using 2-chloro-5-trifluoromethylpyridine (363 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 °C for 15.5 hours. Flash column chromatography (silica gel, gradient elution: 1% EtOAc in hexanes to 2% EtOAc in hexanes) afforded the title compound as a yellow oil (590 mg, 1.78 mmol, 89% yield). IR ν_{max}/cm^{-1} (film): 3055, 3003, 2359, 1955, 1881, 1684, 1594, 1558, 1479, 1281, 938, 578; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.95 (1H, s), 7.76 (1H, d, *J* = 8.1), 7.48-7.31 (10H, m), 7.19 (1H, d, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7 (d, *J* = 2.2 Hz), 146.8 (dd, *J* = 11.7, 4.0 Hz), 135.2 (d, *J* = 9.9), 134.5 (d, *J* = 20.3 Hz), 132.9-132.6 (m), 132.3 (d, *J* = 9.6 Hz), 129.7, 129.0 (d, *J* = 7.5 Hz), 127.3 (d, *J* = 16.1 Hz), 123.7 (q, *J* = 272.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: −62.51; ^{31}P NMR (162

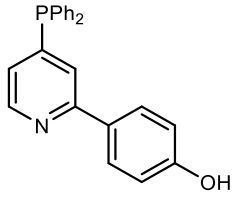
MHz, $CDCl_3$) δ: –2.34; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 332.1, $C_{18}H_{14}F_3NP^+$ requires 332.1.

2-(Diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (6f)



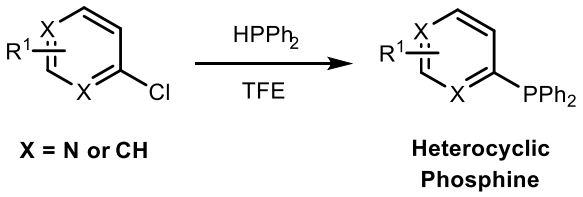
Prepared according to general procedure A' using 2-chloro-5-(thiophen-2-yl)pyridine (391 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 ºC for 21 hours. Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white powder (610 mg, 1.77 mmol, 88% yield). mp 89-91 ºC; IR ν_{max}/cm^{-1} (film): 3053, 1544, 1478, 1458, 1432, 1378, 1267, 1206, 1095, 1025, 850, 828; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.99(1H, d, *J* = 2.0 Hz), 7.74 (1H, dt, *J* = 8.1, 2.0 Hz), 7.47-7.32 (12H, m), 7.14-7.07 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.6 (d, *J* = 3.1 Hz), 147.4 (d, *J* = 13.0 Hz), 140.3, 136.2 (d, *J* = 10.7 Hz), 134.3 (d, *J* = 19.8 Hz), 132.5 (d, *J* = 2.3 Hz), 129.2, 128.9, 128.8 (d, *J* = 6.9 Hz), 128.4, 128.0 (d, *J* = 16.8 Hz), 126.3, 124.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –4.05; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 346.1, $C_{21}H_{17}NPS^+$ requires 346.1.

4-(4-(Diphenylphosphaneyl)pyridin-2-yl)phenol (6g)



Prepared according to general procedure A' using 4-(4-chloropyridin-2-yl)phenol (206 mg, 1.00 mmol), diphenylphosphane (0.21 mL, 1.20 mmol), trifluoromethanesulfonic acid (88 μL, 1.00 mmol), and chlorobenzene (0.5 mL) at 130 ºC for 2 hours. Flash column chromatography (silica gel, gradient elution: 30% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a white powder (293 mg, 0.83 mmol, 83% yield). mp 196-198 ºC; IR ν_{max}/cm^{-1} (film): 3004, 2794, 2663, 2591, 2479, 1608, 1579, 1518, 1435, 1376, 1278, 1241, 1174, 1000, 824; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.76 (1H, s), 8.54 (1H, dd, *J* = 5.1, 2.5 Hz), 7.76 (2H, d, *J* = 8.7 Hz), 7.53 (1H, d, *J* = 7.6 Hz), 7.50–7.41 (m, 6H), 7.41–7.29 (m, 4H), 6.91 (1H, ddd, *J* = 6.2, 4.9, 1.4 Hz), 6.82 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.7, 155.9 (d, *J* = 5.4 Hz), 149.2 (d, *J* = 4.1 Hz), 148.6 (d, *J* = 17.3 Hz), 134.7 (d, *J* = 10.4 Hz), 133.8 (d, *J* = 20.3 Hz), 129.7, 129.3–128.6 (2C, m), 127.9, 124.3 (d, *J* = 13.0 Hz), 122.1 (d, *J* = 18.8 Hz), 115.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –6.32; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 356.2, $C_{23}H_{19}NOP^+$ requires 356.1.

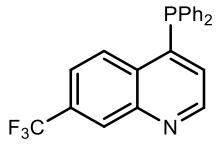
A 3.3.5 General Procedure B' (Heterocyclic Phosphine Synthesis: Quinolines and Diazines)



An oven dried 8 mL vial (< 1.0 mmol) or 15 mL pressure tube (1.0-4.0 mmol) equipped with a stir bar was charged with the heterocycle (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, and TFE (0.4 M) was added, followed by diphenylphosphine (1.2 equiv). The reaction was heated to 80 ºC and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of

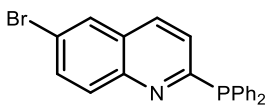
brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl phosphine product.

4-(diphenylphosphaneyl)-7-(trifluoromethyl)quinoline (6h)



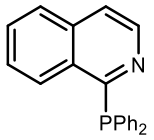
Prepared according to general procedure B' using 4-chloro-7-(trifluoromethyl)quinoline (926 mg, 4.00 mmol), diphenylphosphane (0.84 mL, 4.80 mmol), and TFE (10.0 mL) at 80 °C for 16 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as an faint yellow solid (1.30 g, 3.41 mmol, 85% yield). mp 86-89 °C; IR ν_{max}/cm^{-1} (film): 3074, 3052, 3016, 1569, 1505, 1478, 1433, 1206, 856, 600, 529; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.84 (1H, dd, *J* = 4.4, 1.2 Hz), 8.44 (1H, s), 8.34 (1H, dd, *J* = 8.8, 3.4 Hz), 7.62 (1H, dd, *J* = 8.8, 2.0 Hz), 7.46-7.27 (10H, m), 6.93 (1H, t, *J* = 4.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.1, 147.6 (d, *J* = 22.5 Hz), 146.8 (d, *J* = 2.7 Hz), 134.5 (d, *J* = 20.5 Hz), 133.9 (d, *J* = 8.3 Hz), 131.5 (d, *J* = 3.5 Hz), 131.4 (d, *J* = 47.7 Hz), 129.2, 129.2 (d, *J* = 7.6 Hz), 128.2-127.9 (m), 127.6 (d, *J* = 22.0 Hz), 127.1, 124.0 (q, *J* = 272.5 Hz), 122.6-122.2 (m); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.75 ^{31}P NMR (162 MHz, $CDCl_3$) δ: –14.95; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 382.2, $C_{22}H_{16}F_3NP^+$ requires 382.1.

6-Bromo-2-(diphenylphosphaneyl)quinoline (6i)



Prepared according to general procedure B using 2-chloro-6-bromoquinoline (485 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and TFE (5.0 mL) at 80 °C for 19 hours. Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the title compound as an orange viscous oil (748 mg, 1.90 mmol, 95% yield). IR ν_{max}/cm^{-1} (film): 3047, 3006, 2967, 2929, 2872, 223, 1963, 1575, 1537, 1286, 999; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (1H, d, *J* = 9.01), 7.95-7.88 (2H, m), 7.76 (1H, dd, *J* = 9.0, 2.2 Hz), 7.52-7.30 (10H, m), 7.20 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.9 (d, *J* = 1.54 Hz), 147.2 (d, *J* = 14.4 Hz), 136.1 (d, *J* = 11.1 Hz), 134.4 (d, *J* = 19.8 Hz) 134.4 (d, *J* = 2.6 Hz), 133.3, 131.5, 129.8, 129.3, 128.8 (d, *J* = 7.2 Hz), 128.0, 125.2 (d, *J* = 14.7 Hz), 120.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ: −1.83; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 392.1, $C_{21}H_{16}BrNP^+$ requires 392.0.

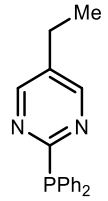
1-(diphenylphosphaneyl)isoquinoline (6j)



Prepared according to general procedure B using 1-chloro-isoquinoline (328 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and TFE (5.0 mL) at 80 °C for 16.5 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as an white crystalline solid (579 mg, 1.86 mmol, 93% yield). mp 143-145; °C IR ν_{max}/cm^{-1} (film): 3069, 3046, 3004, 2924, 2361, 2340, 1577, 1543, 1492, 1434, 1304, 828, 694, 672, 546, 539, 527; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66-8.56 (2 H, m), 7.82 (1H, d, *J* = 8.2 Hz), 7.65 (1H, t, *J* = 7.5 Hz), 7.58 (1H, d, *J* = 5.6 Hz), 7.52 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz), 7.45-7.29 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8 (d, *J* = 10.0 Hz), 143.4 (d, *J* = 4.1 Hz), 136.1 (d, *J* = 6.9 Hz), 135.5 (d, *J* = 4.0 Hz), 134.6 (d, *J* = 20.0 Hz), 132.2 (d, *J* = 29.0 Hz), 130.1 (d, *J* = 1.3 Hz), 129.0, 128.5 (d, *J* =

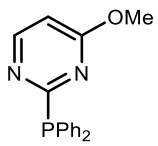
7.6 Hz), 127.5 (d, J = 2.0 Hz), 127.3 (d, J = 1.8 Hz), 127.1 (d, J = 23.0 Hz), 120.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –8.33; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 314.2, $C_{21}H_{17}NP^+$ requires 314.1.

2-(Diphenylphosphaneyl)-5-ethylpyrimidine (6k)



Prepared according to general procedure B using 2-chloro-5-ethylpyrimidine (243 μL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and TFE (5.0 mL) at 80 °C for 19 hours. Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a white crystalline solid (478 mg, 1.64 mmol, 82% yield). mp 78-80 °C; IR ν_{max}/cm^{-1} (film): 3070, 3045, 3006, 2929, 1962, 1536, 1208, 1100, 816; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (2H, s), 7.59-7.43 (4H, m), 7.42-7.30 (6H, m), 2.62 (2H, q, J = 7.63 Hz), 1.27 (3H, t, J = 7.63 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.8 (d, J = 12.4 Hz), 156.3 (d, J = 6.7 Hz), 135.9 (d, J = 20.1 Hz), 134.6 (d, J = 20.1 Hz), 134.1, 129.3, 128.6 (d, J = 7.6 Hz), 23.6, 14.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –0.70; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 293.2, $C_{18}H_{18}N_2P^+$ requires 293.2.

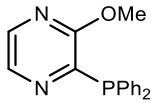
2-(Diphenylphosphaneyl)-4-methoxypyrimidine (6l)



Prepared according to general procedure B using 2-chloro-4-methoxypyrimidine (723 mg, 5.00 mmol), diphenylphosphane (1.04 mL, 6.00 mmol, and TFE (13.50 mL) at 80 °C for 19.5 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a clear oil (1.10 g, 3.75

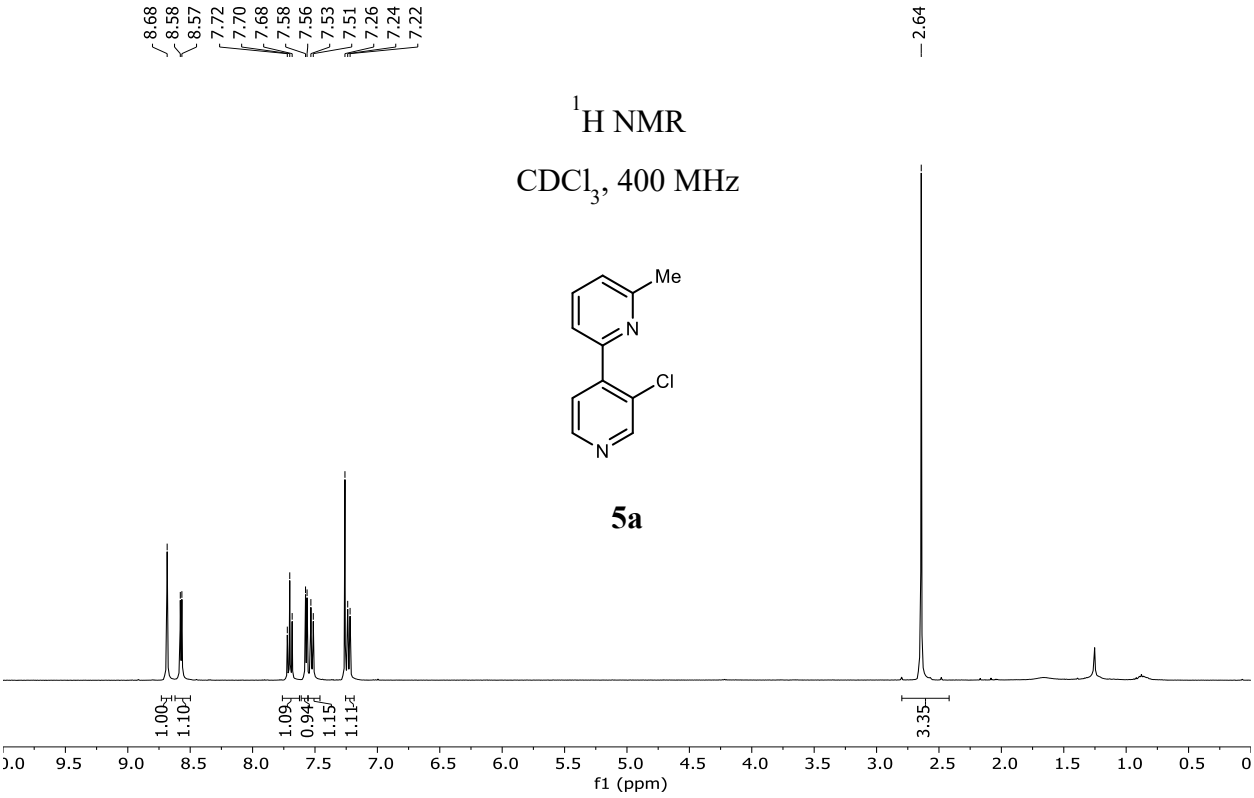
mmol, 75% yield). IR ν_{max}/cm^{-1} (film): 3052, 3002, 2950, 2363, 2153, 1963, 1907, 1825, 1683, 1610, 782, 617, 578; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (1H, dd, *J* = 5.8, 0.7 Hz), 7.59-7.47 (4H, m), 7.40-7.30 (6H, m), 6.54 (1H, dd, *J* = 5.8, 0.9 Hz), 3.75 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.0 (d, *J* = 12.4 Hz), 168.2 (d, *J* = 6.2 Hz), 156.8 (d, *J* = 7.6 Hz), 135.7 (d, *J* = 7.6 Hz), 134.7 (d, *J* = 19.8 Hz), 129.1, 128.3 (d, *J* = 7.6 Hz), 106.1 (d, *J* = 2.0 Hz), 53.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ: −1.62; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 295.1, $C_{17}H_{16}N_2OP^+$ requires 295.1.

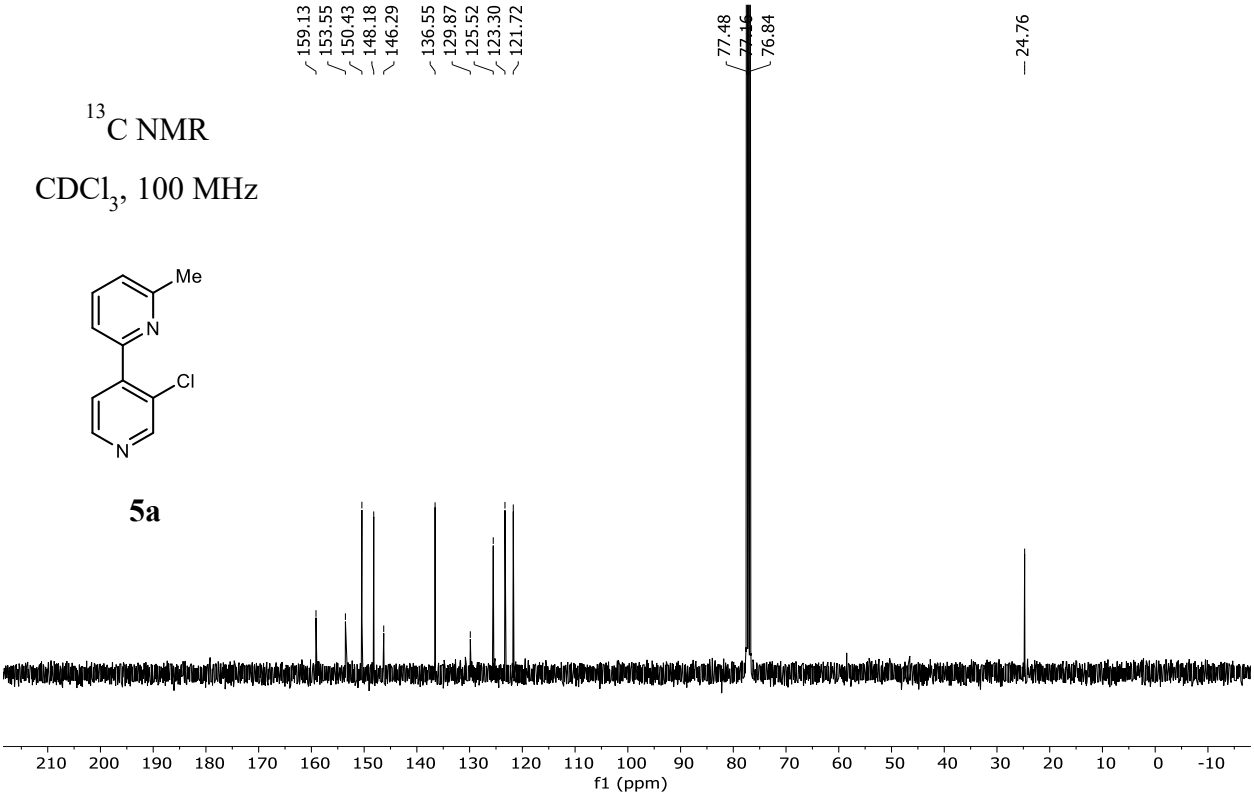
2-(Diphenylphosphaneyl)-3-methoxypyrazine (2m)

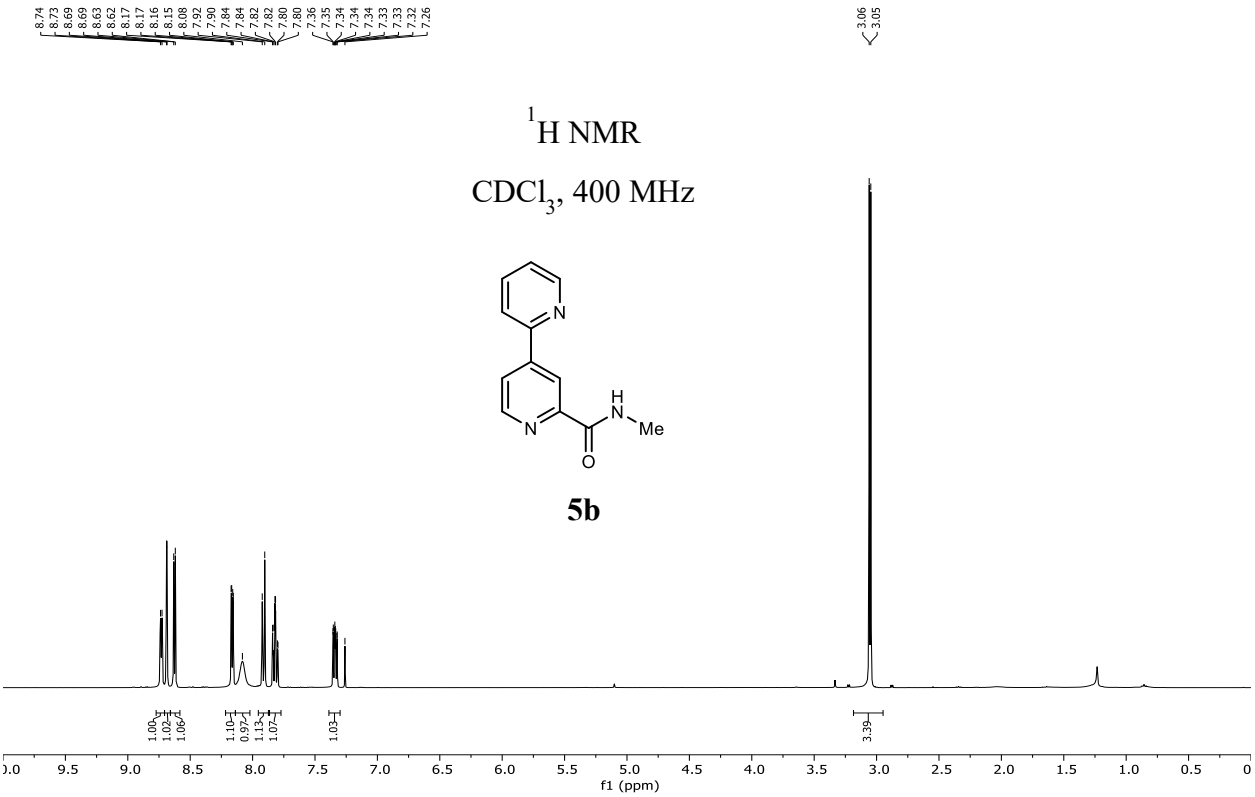


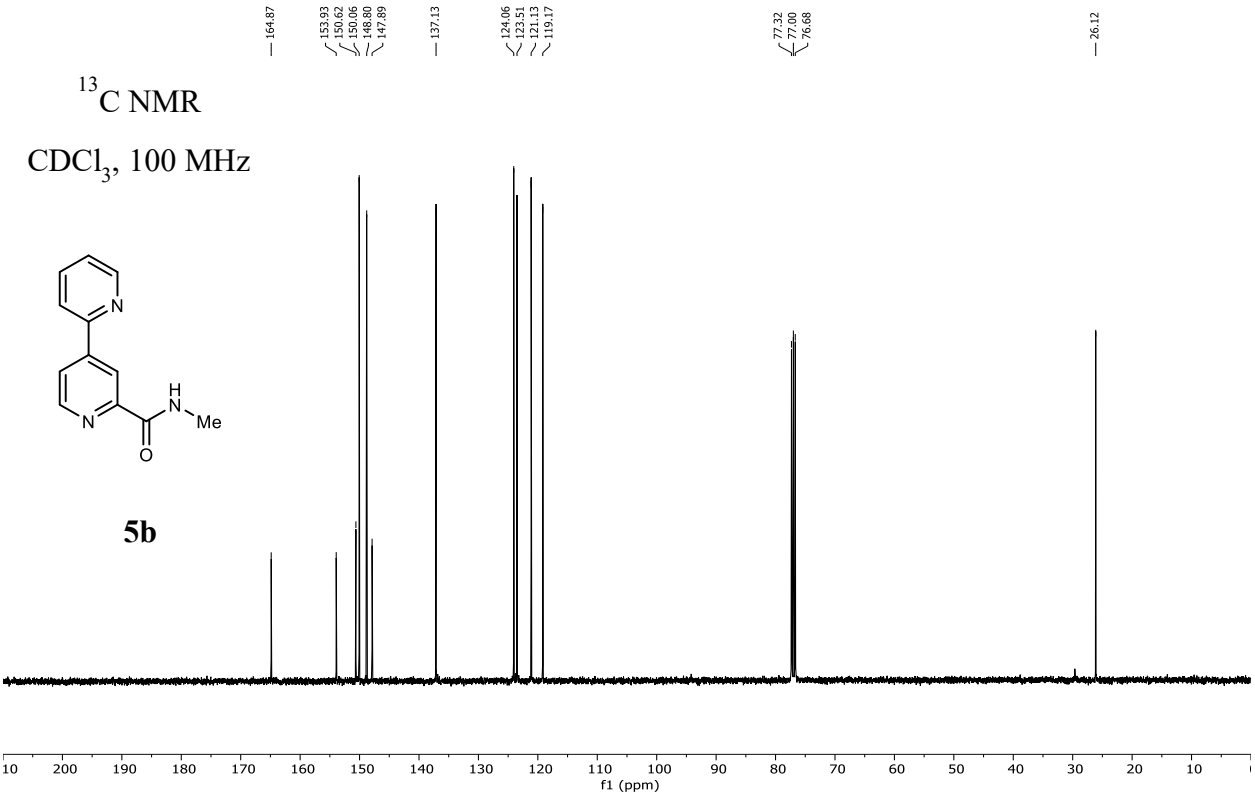
Prepared according to general procedure B using 2-chloro-3-methoxypyrazine (434 mg, 3.00 mmol), diphenylphosphane (0.63 mL, 3.60 mmol, and TFE (7.5 mL) at 80 °C for 2 hours. Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white powder (549 mg, 1.87 mmol, 62% yield). mp 104-105 °C; IR ν_{max}/cm^{-1} (film): 3052, 2943, 1515, 1479, 1454, 1434, 1368, 1353, 1297, 1220, 1179, 1157, 1099, 999, 866, 747; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (1H, d, *J* = 2.7 Hz), 8.01 (1H, d, *J* = 2.8 Hz), 7.44–7.29 (10H, m), 3.86 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.7 (d, *J* = 21.8 Hz), 148.6 (d, *J* = 13.4 Hz), 139.6, 137.6, 134.6 (d, *J* = 7.2 Hz), 134.3 (d, *J* = 20.2 Hz), 129.0, 128.3 (d, *J* = 7.6 Hz), 53.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ: −10.32; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 295.1, $C_{17}H_{16}N_2OP^+$ requires 295.1.

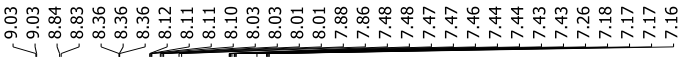
A 3.4 Spectra


8.68
8.58
8.57
7.72
7.70
7.68
7.58
7.56
7.53
7.51
7.26
7.24
7.22
2.64
1H NMR
CDCl3, 400 MHz
Me
N
Cl
N
5a
1.00
1.10
1.09
0.94
1.15
1.11
3.35
f1 (ppm)


159.13
153.55
150.43
148.18
146.29
136.55
129.87
125.52
123.30
121.72
77.48
77.16
76.84
24.76
13C NMR
CDCl3, 100 MHz
Me
N
Cl
N
5a
f1 (ppm)

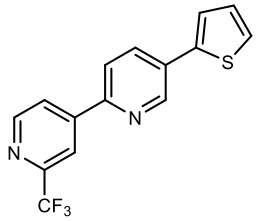

8.74
8.73
8.69
8.69
8.63
8.62
8.17
8.17
8.16
8.15
8.08
7.92
7.90
7.84
7.84
7.82
7.82
7.80
7.80
7.36
7.35
7.34
7.34
7.34
7.33
7.33
7.32
7.26
3.06
3.05
1H NMR
CDCl3, 400 MHz
N
N
H
N
Me
O
5b
1.00
1.02
1.06
1.10
0.97
1.13
1.07
1.03
3.39
f1 (ppm)


164.87
153.93
150.62
150.06
148.80
147.89
137.13
124.06
123.51
121.13
119.17
77.32
77.00
76.68
26.12
13C NMR
CDCl3, 100 MHz
N
N
H
N
Me
O
5b
f1 (ppm)

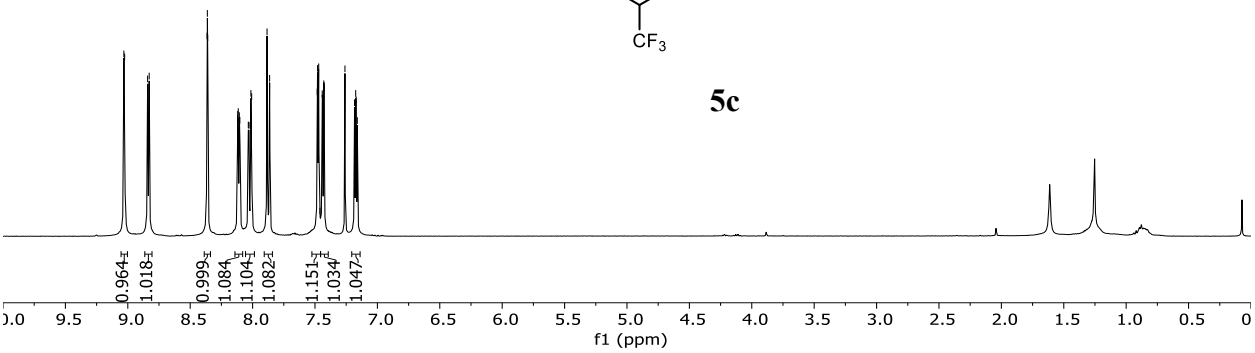


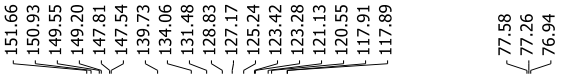
^{1}H NMR

$CDCl_3$, 400 MHz



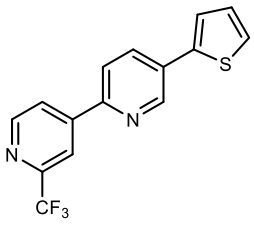
5c



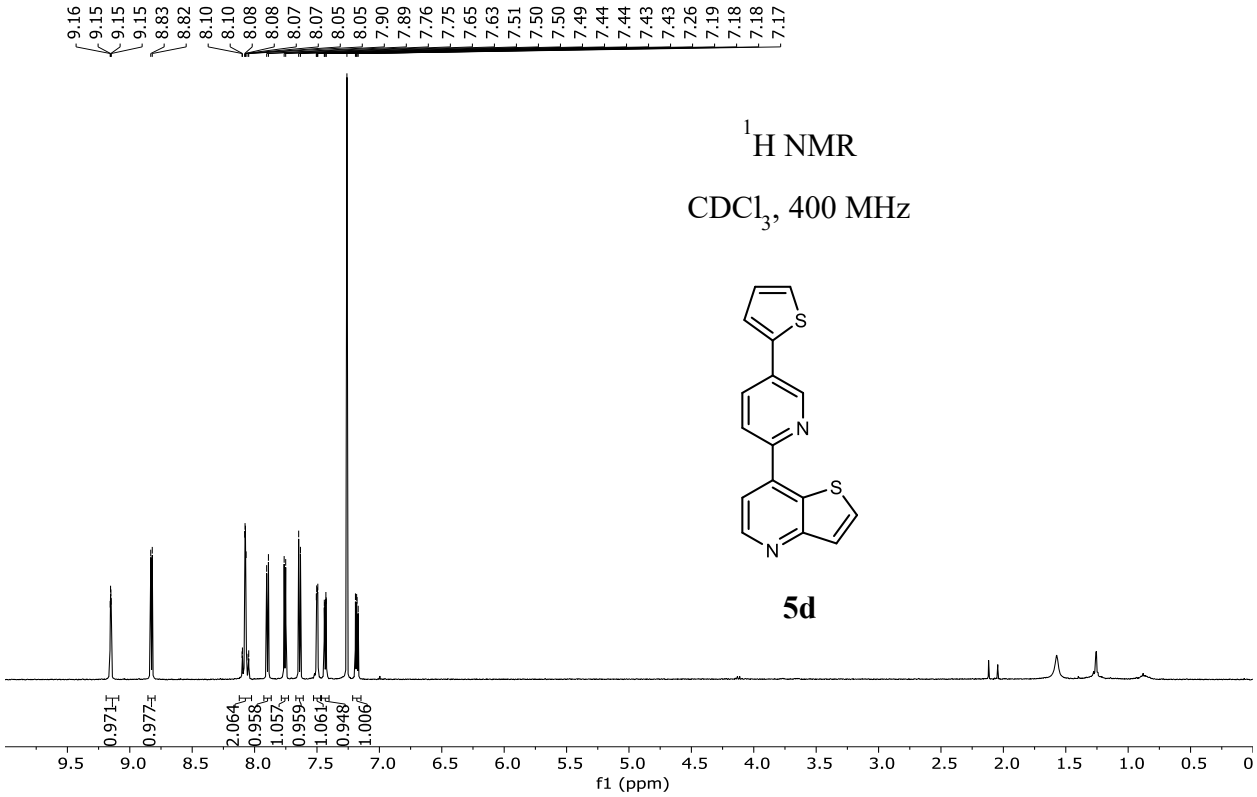


^{13}C NMR

$CDCl_3$, 100 MHz



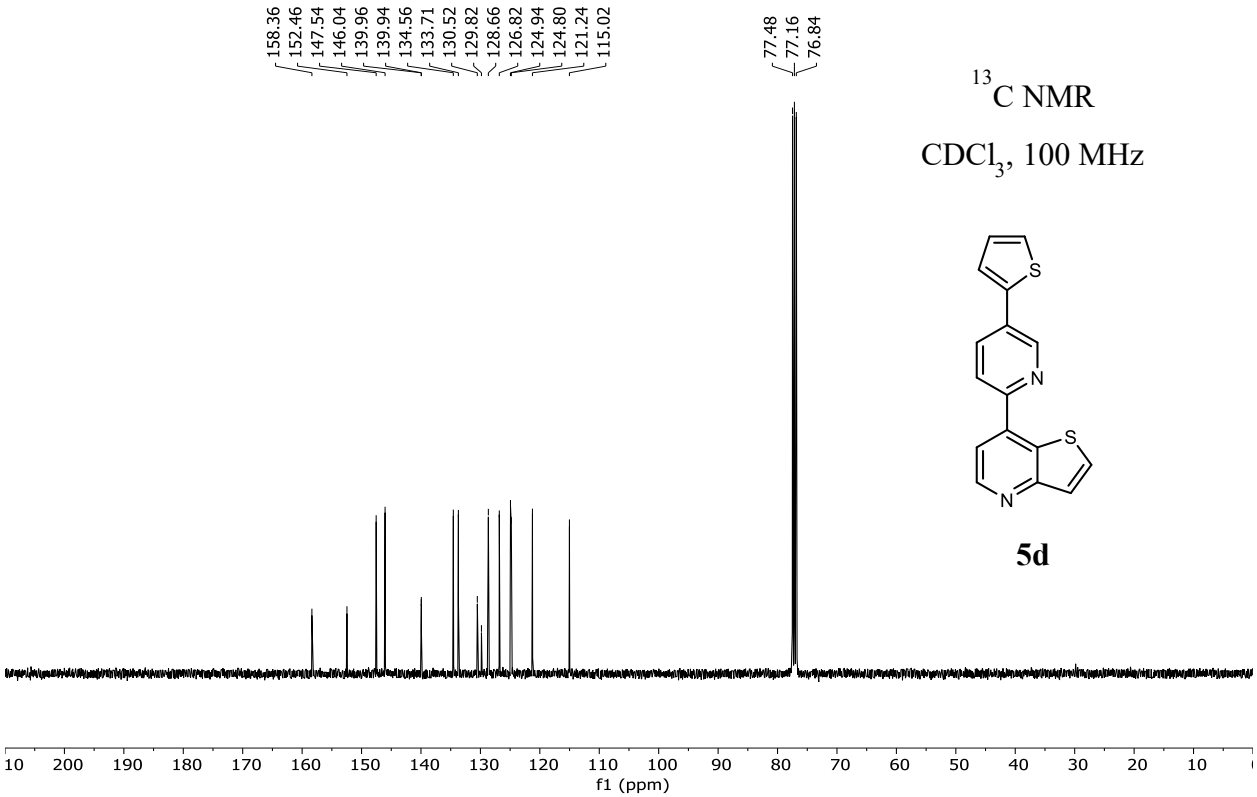
5c



^{1}H NMR

$CDCl_3$, 400 MHz

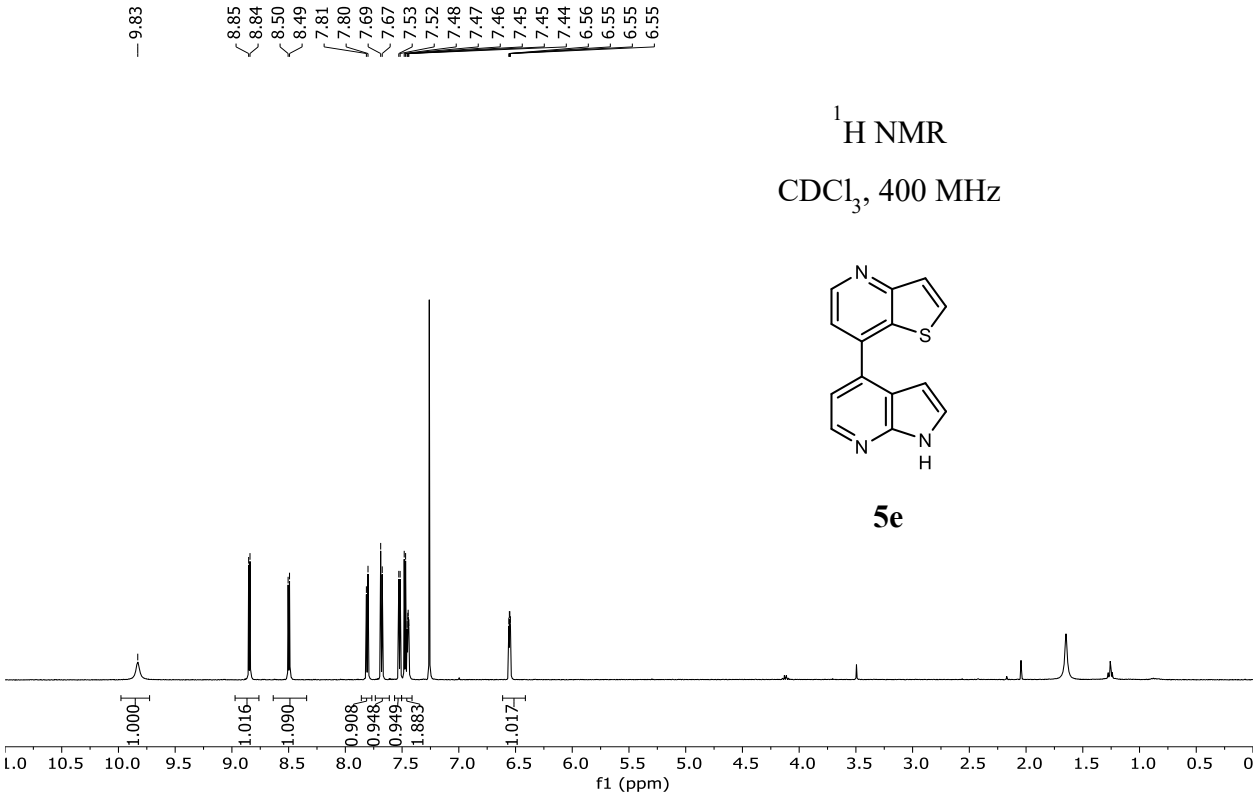
5d

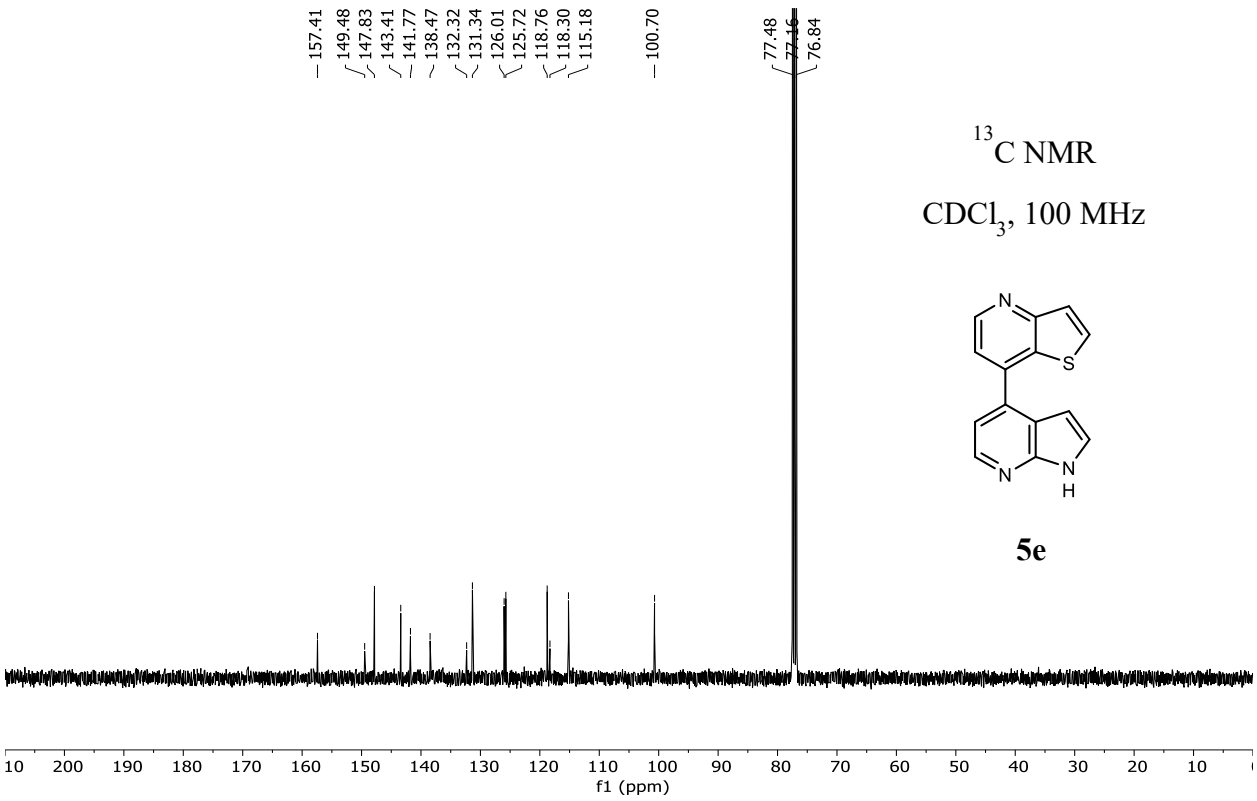


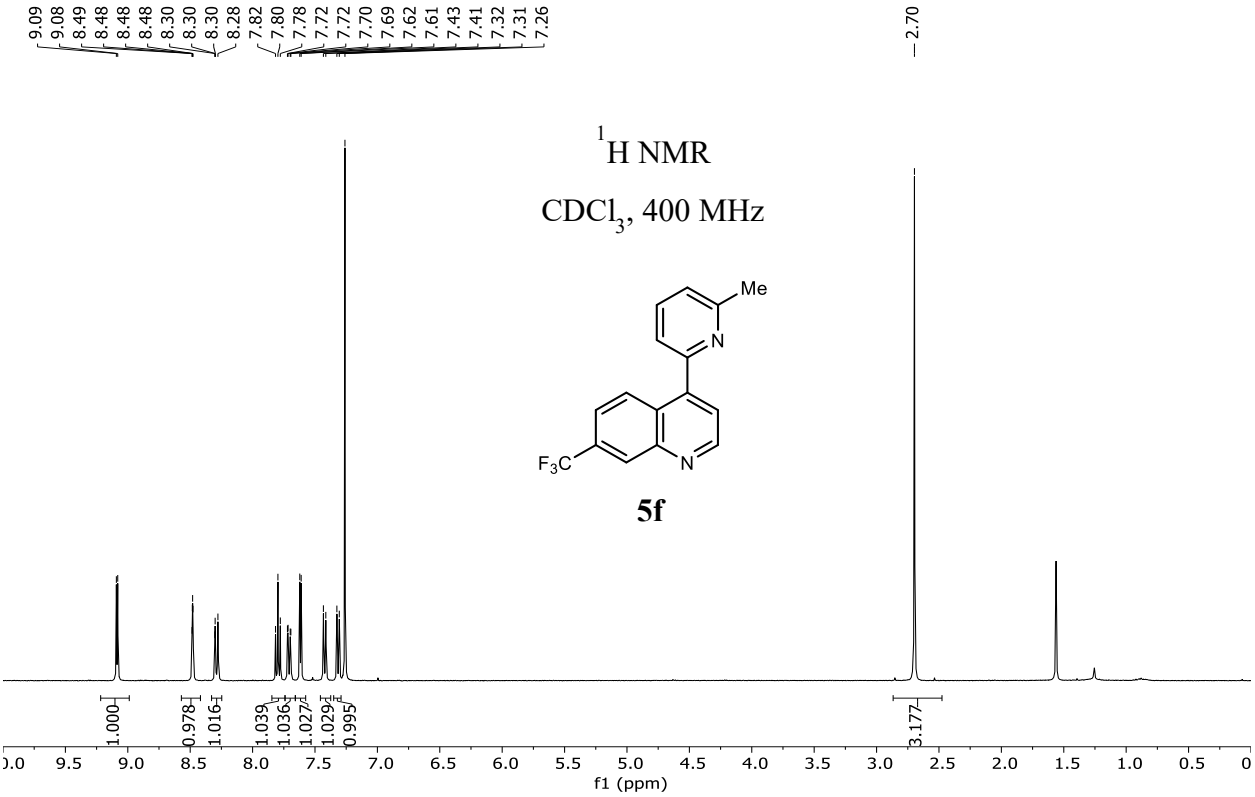
^{13}C NMR

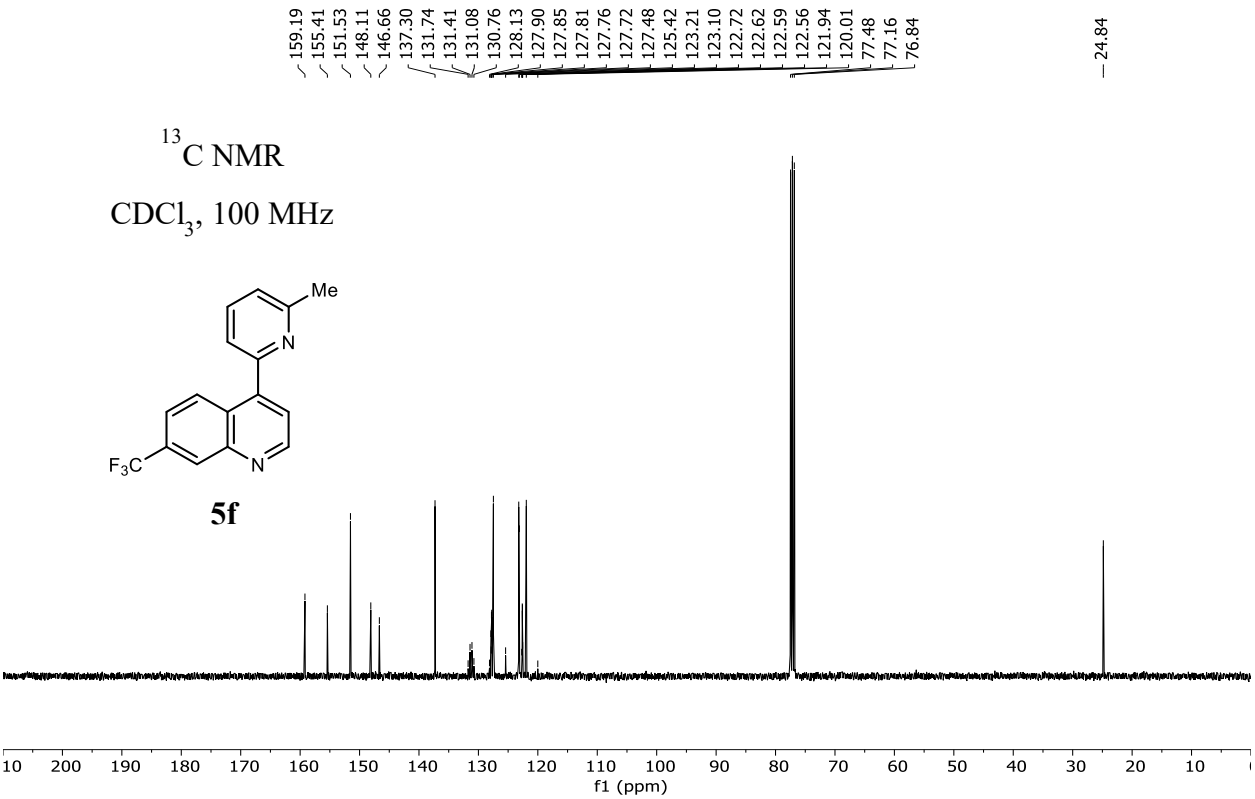
$CDCl_3$, 100 MHz

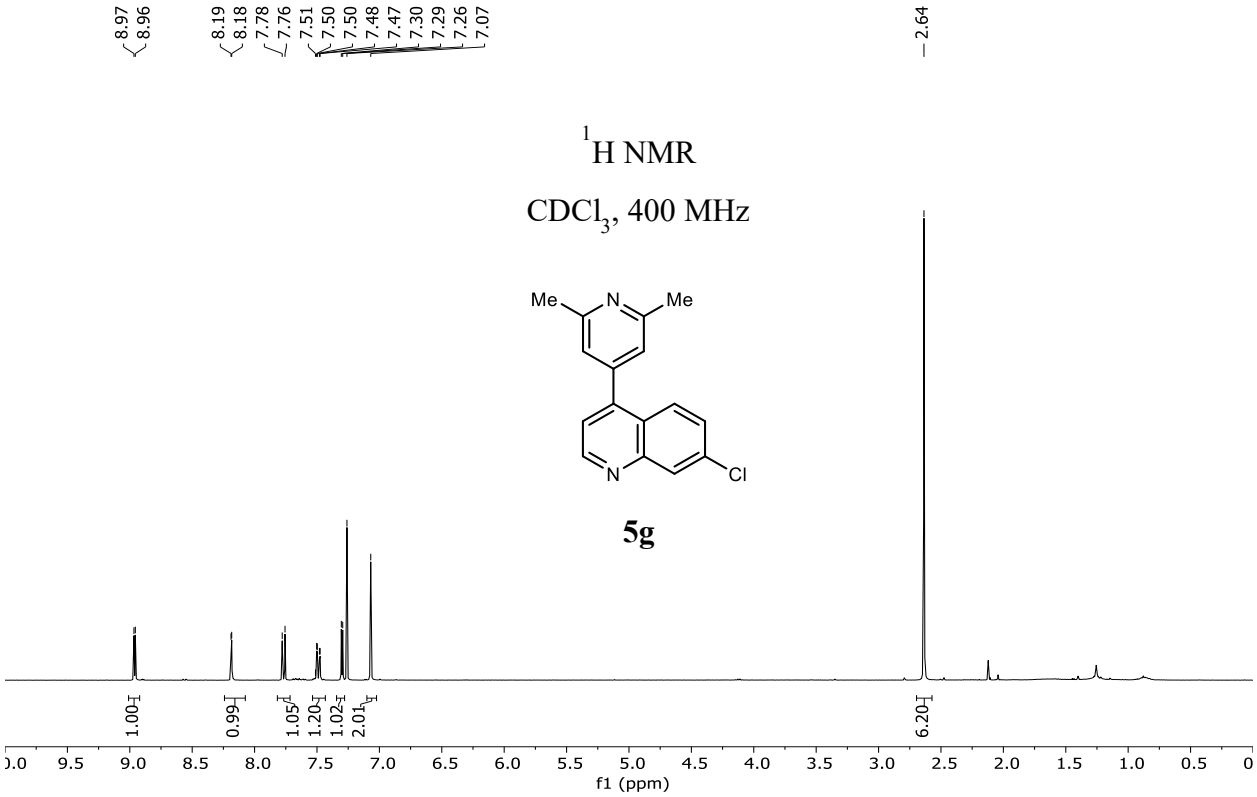
5d

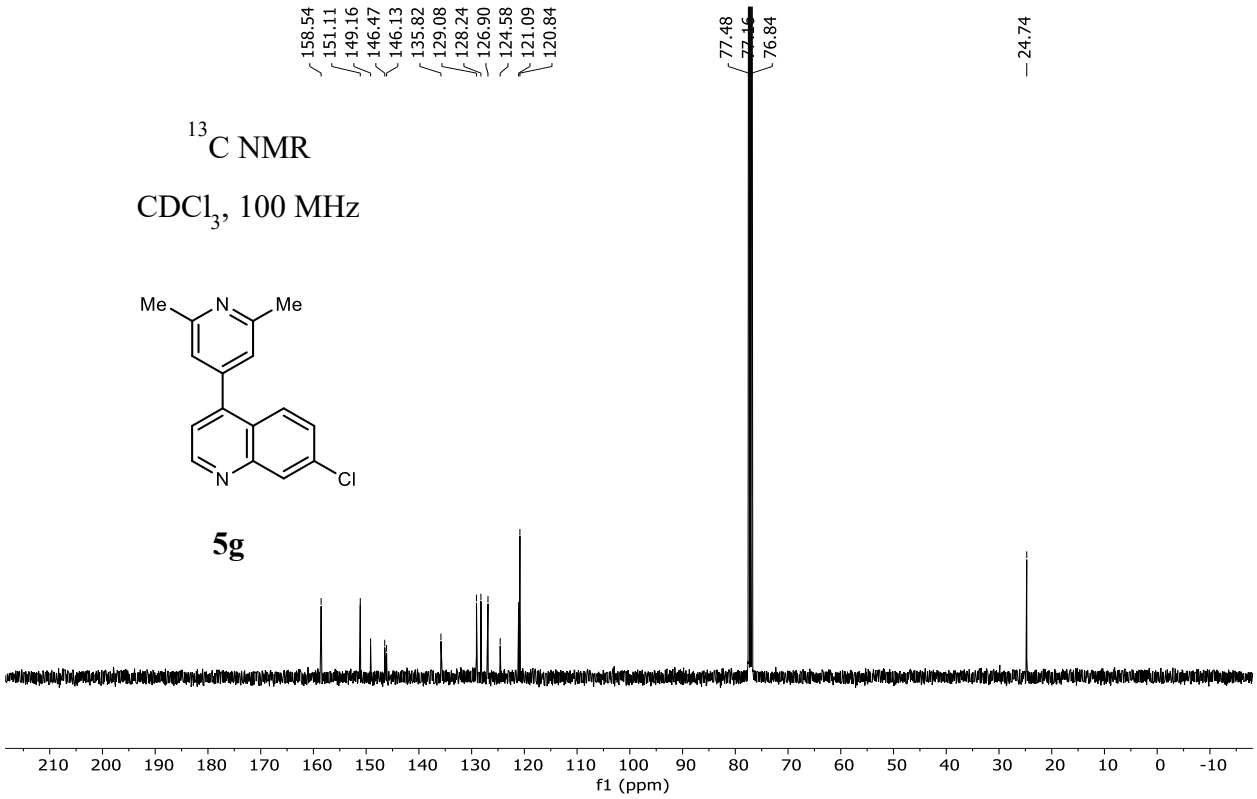

9.83
8.85
8.84
8.50
8.49
7.81
7.80
7.69
7.67
7.53
7.52
7.48
7.47
7.46
7.45
7.45
7.44
6.56
6.55
6.55
6.55
1H NMR
CDCl3, 400 MHz
5e
1.000
1.016
1.090
0.908
0.948
0.949
1.883
1.017
f1 (ppm)

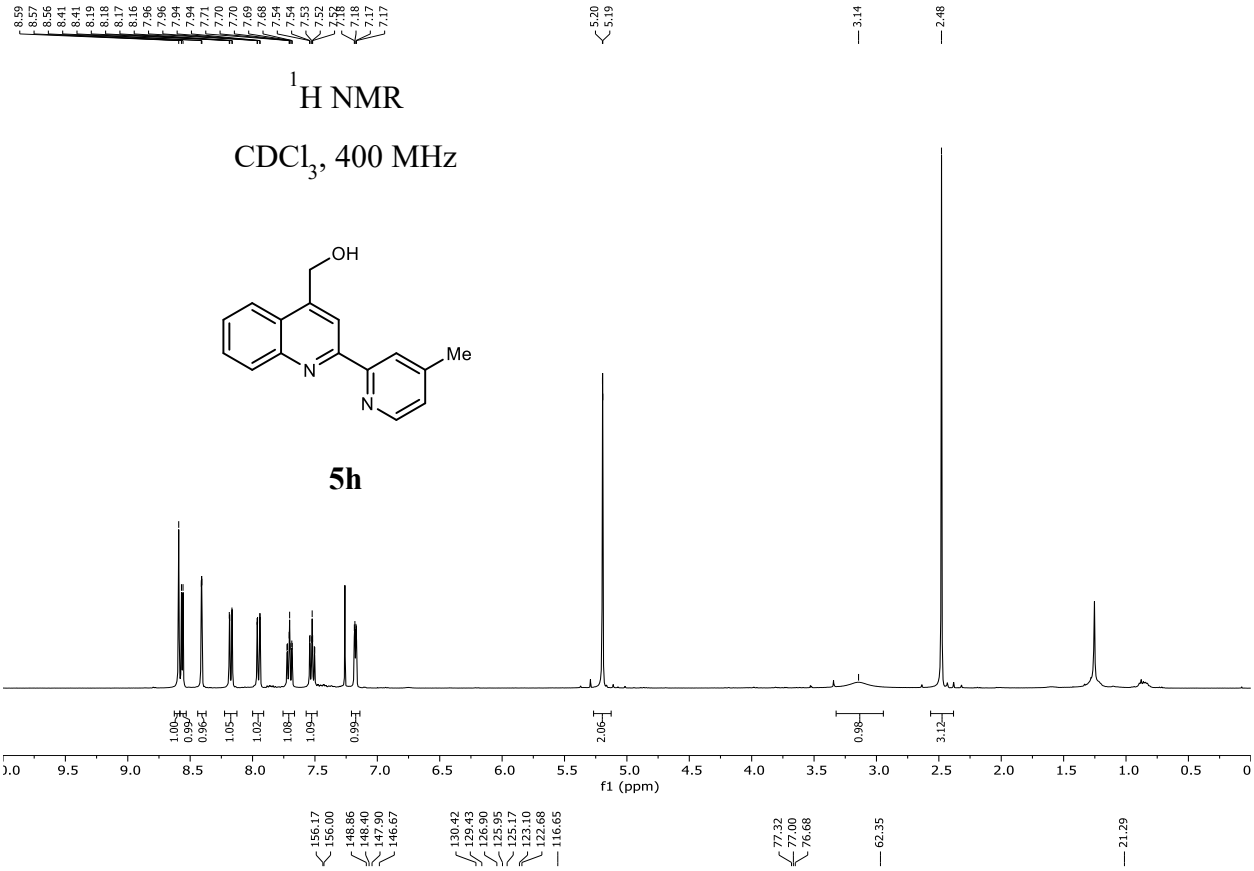

157.41
149.48
147.83
143.41
141.77
138.47
132.32
131.34
126.01
125.72
118.76
118.30
115.18
100.70
77.48
77.16
76.84
13C NMR
CDCl3, 100 MHz
5e
f1 (ppm)


9.09
9.08
8.49
8.48
8.48
8.48
8.30
8.30
8.30
8.28
7.82
7.80
7.78
7.72
7.72
7.70
7.69
7.62
7.61
7.43
7.41
7.32
7.31
7.26
2.70
1H NMR
CDCl3, 400 MHz
Me
N
F3C
N
5f
1.000
0.978
1.016
1.039
1.036
1.027
1.029
0.995
3.177
f1 (ppm)


159.19
155.41
151.53
148.11
146.66
137.30
131.74
131.41
131.08
130.76
128.13
127.90
127.85
127.81
127.76
127.72
127.48
125.42
123.21
123.10
122.72
122.62
122.59
122.56
121.94
120.01
77.48
77.16
76.84
24.84
13C NMR
CDCl3, 100 MHz
Me
N
F3C
N
5f
f1 (ppm)


8.97
8.96
8.19
8.18
7.78
7.76
7.51
7.50
7.50
7.48
7.47
7.30
7.29
7.26
7.07
2.64
1H NMR
CDCl3, 400 MHz
Me
N
Me
N
Cl
5g
1.00
0.99
1.05
1.20
1.02
2.01
6.20
f1 (ppm)

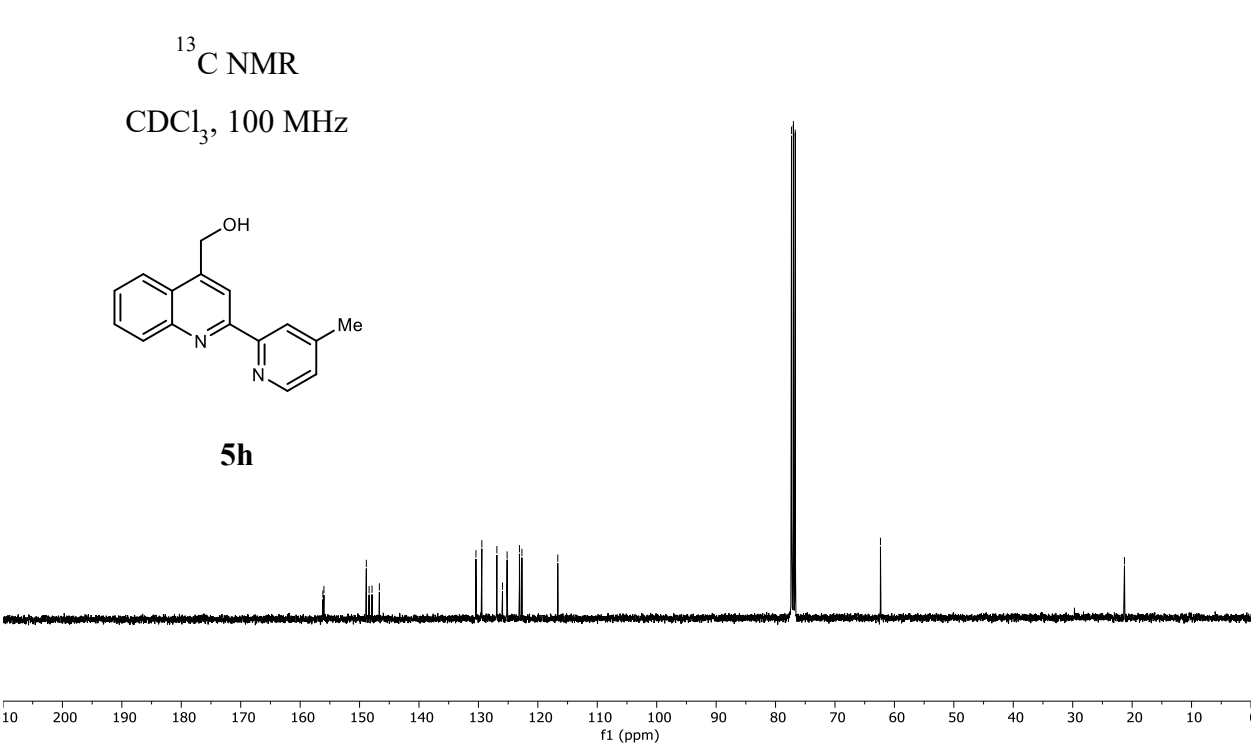

158.54
151.11
149.16
146.47
146.13
135.82
129.08
128.24
126.90
124.58
121.09
120.84
77.48
77.16
76.84
24.74
13C NMR
CDCl3, 100 MHz
Me
N
Me
N
Cl
5g
f1 (ppm)



^{1}H NMR

$CDCl_3$, 400 MHz

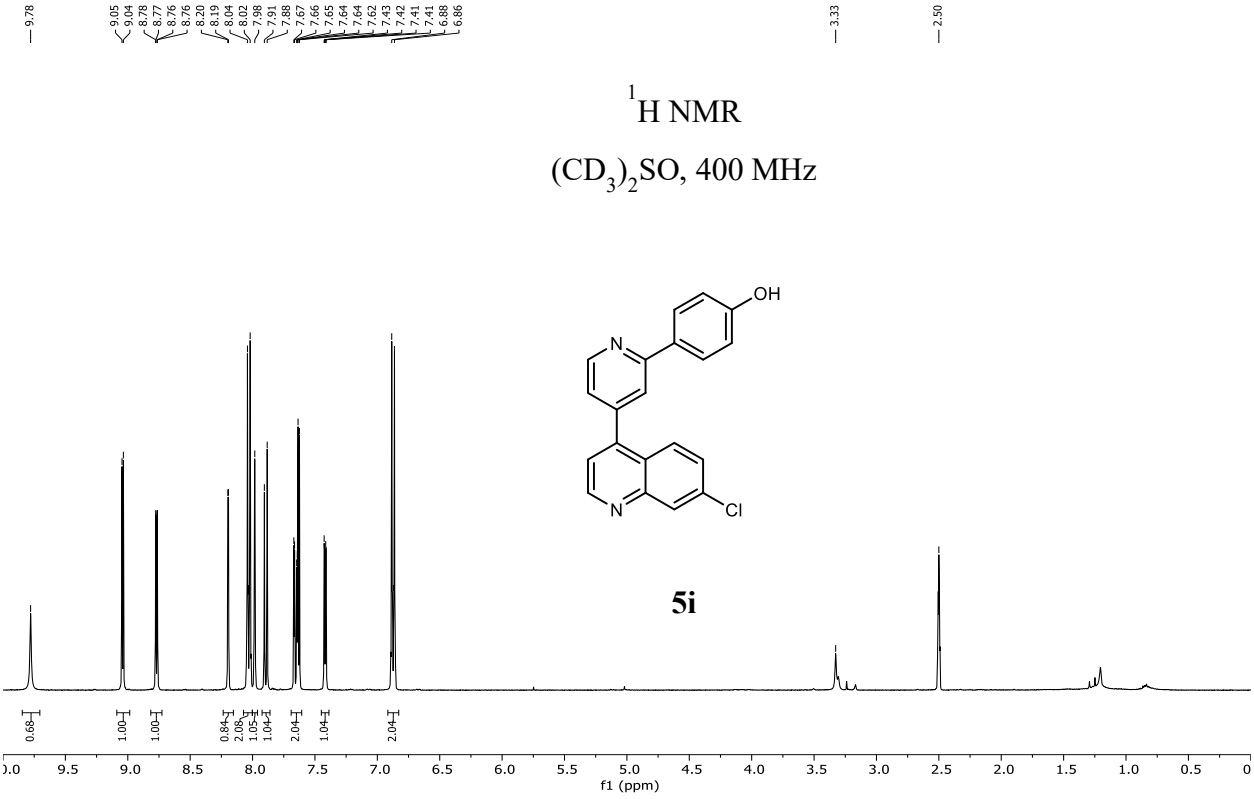
5h



^{13}C NMR

$CDCl_3$, 100 MHz

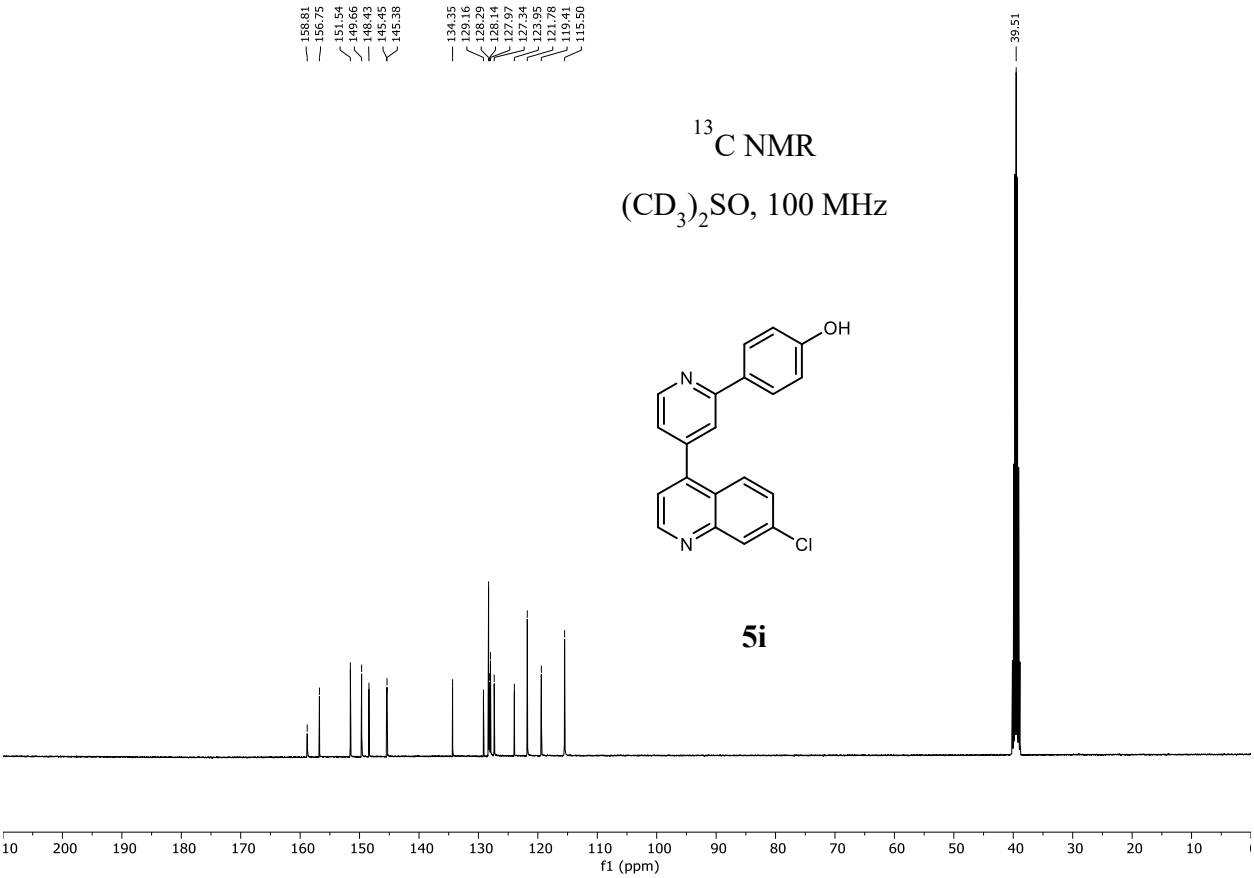
5h



^{1}H NMR

$(CD_3)_2SO$, 400 MHz

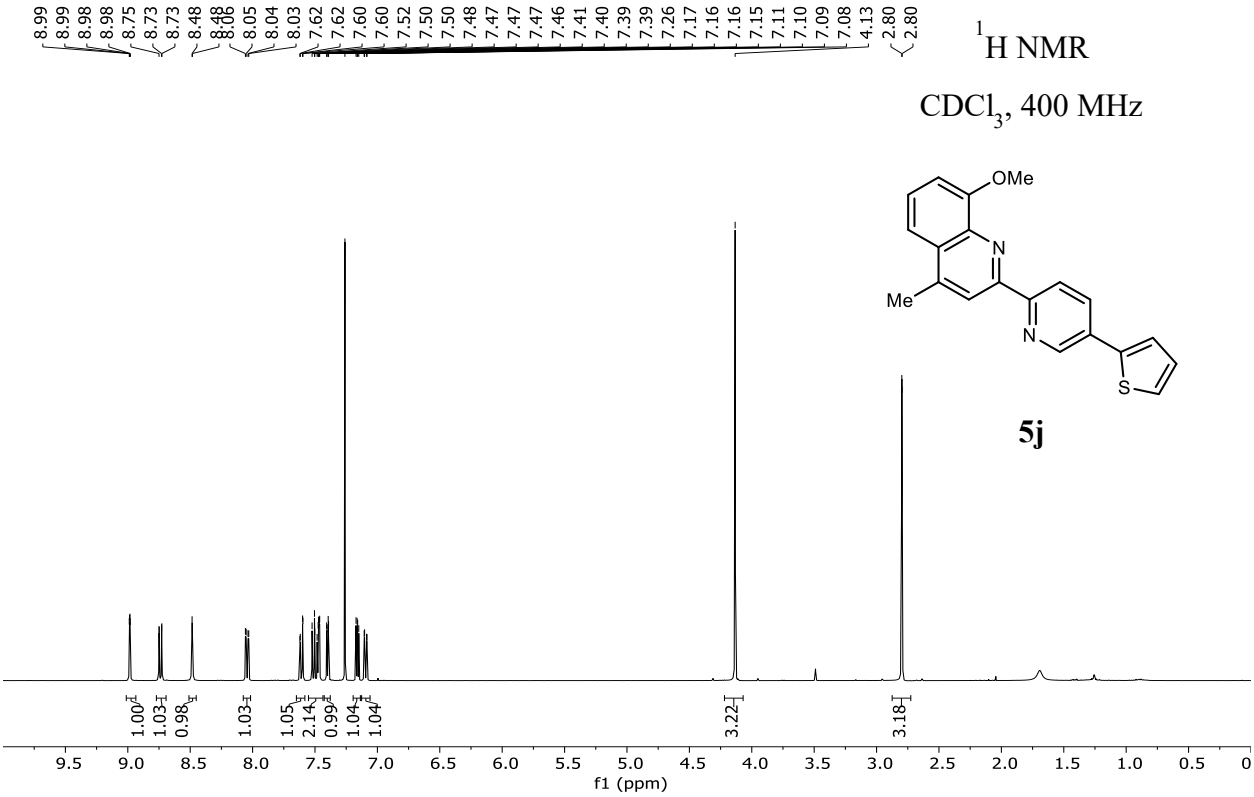
5i

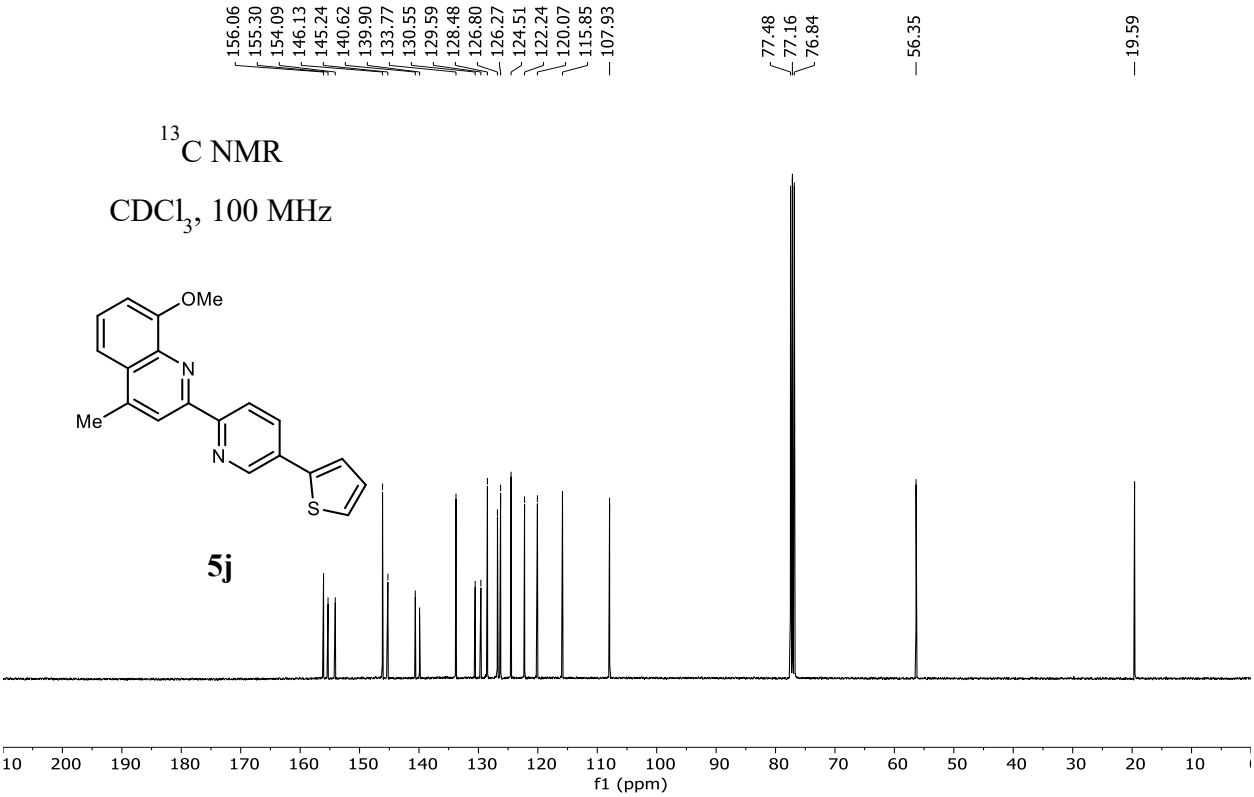


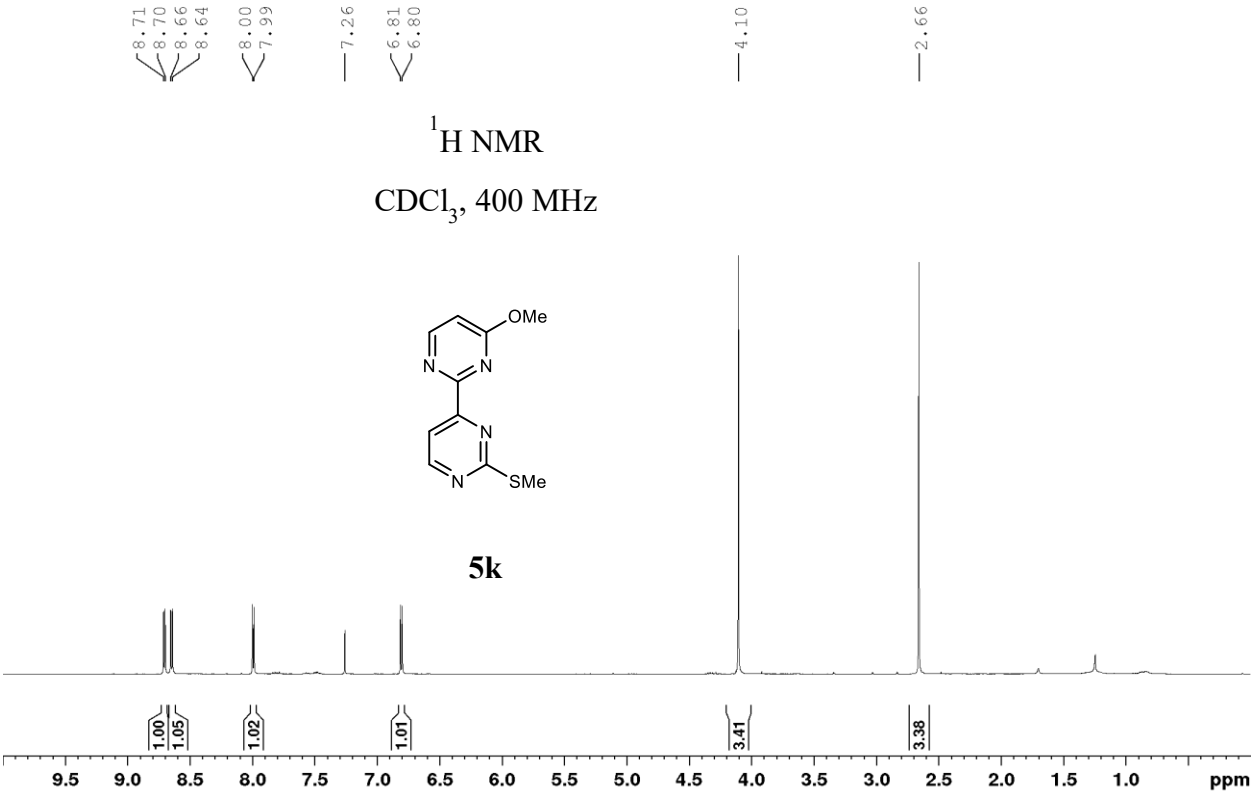
^{13}C NMR

$(CD_3)_2SO$, 100 MHz

5i


8.99 8.99 8.98 8.98 8.75 8.73 8.73 8.48 8.48 8.06 8.05 8.04 8.03 7.62 7.62 7.60 7.60 7.52 7.50 7.50 7.48 7.47 7.47 7.46 7.41 7.40 7.39 7.39 7.26 7.17 7.16 7.16 7.15 7.11 7.10 7.09 7.08 4.13 2.80 2.80
1H NMR
CDCl3, 400 MHz
OMe
N
Me
N
S
5j
1.00 1.03 0.98 1.03 1.05 2.14 0.99 1.04 1.04 3.22 3.18
f1 (ppm)

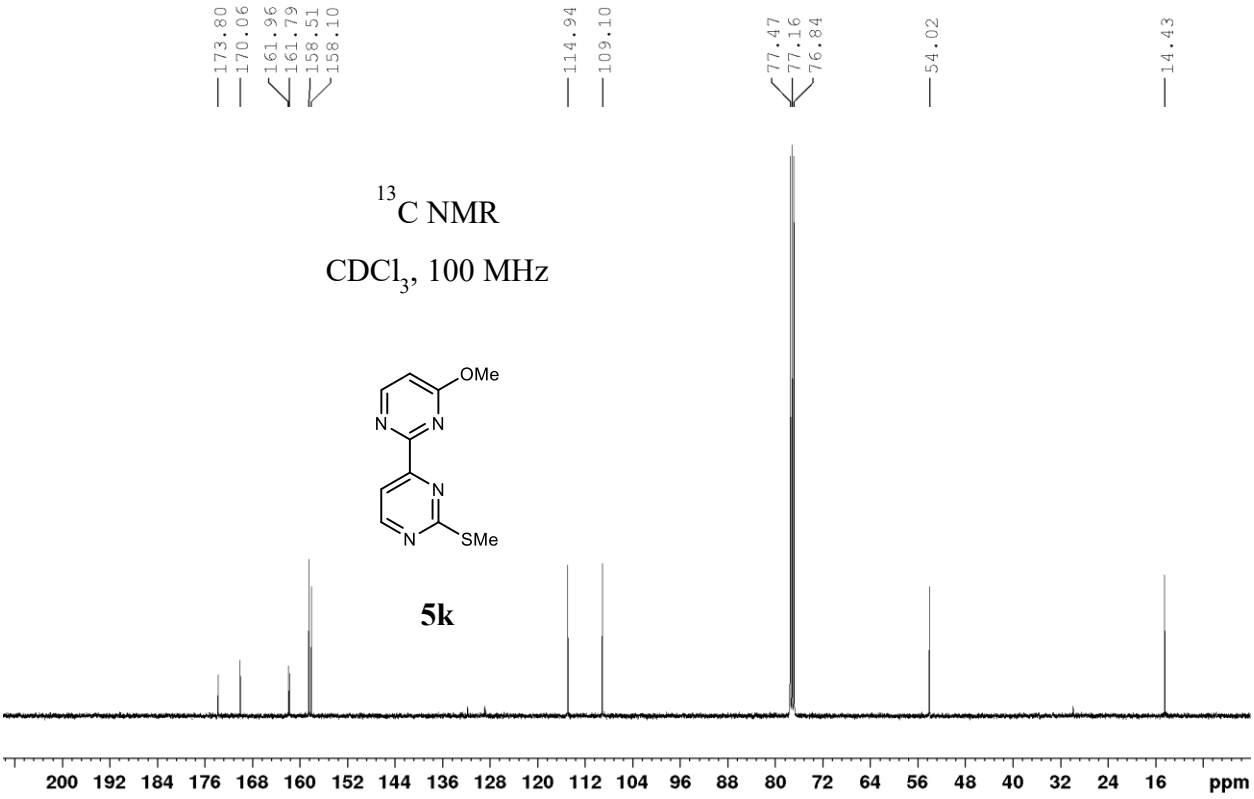

156.06 155.30 154.09 146.13 145.24 140.62 139.90 133.77 130.55 129.59 128.48 126.80 126.27 124.51 122.24 120.07 115.85 107.93
77.48 77.16 76.84
56.35
19.59
13C NMR
CDCl3, 100 MHz
OMe
N
Me
N
S
5j
f1 (ppm)



^{1}H NMR

$CDCl_3$, 400 MHz

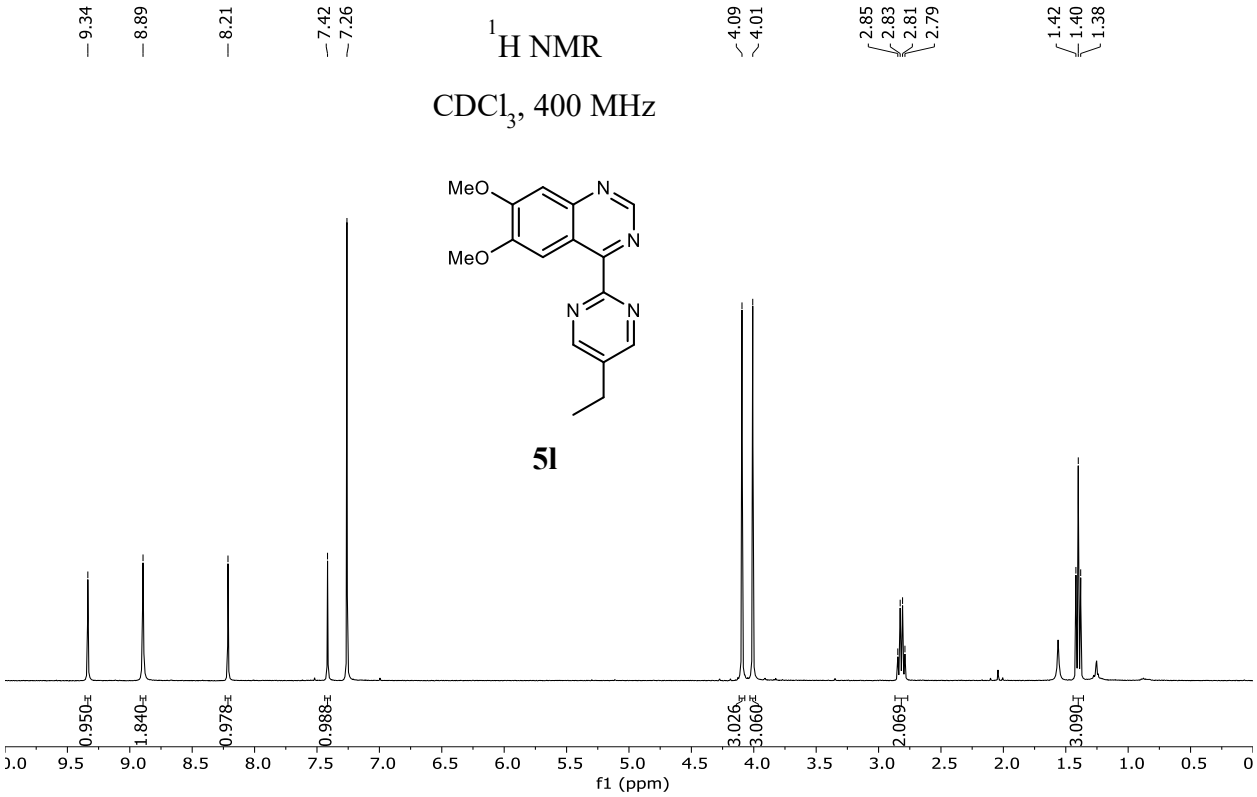
5k

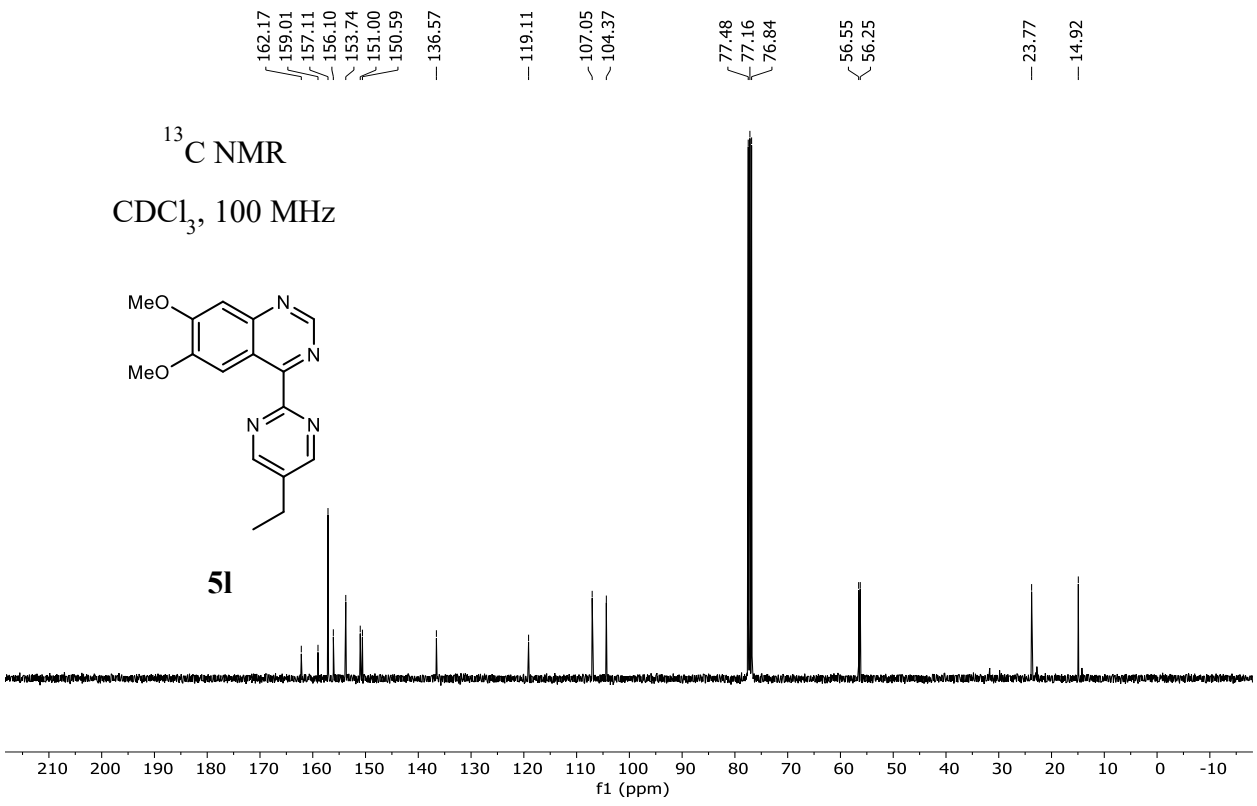


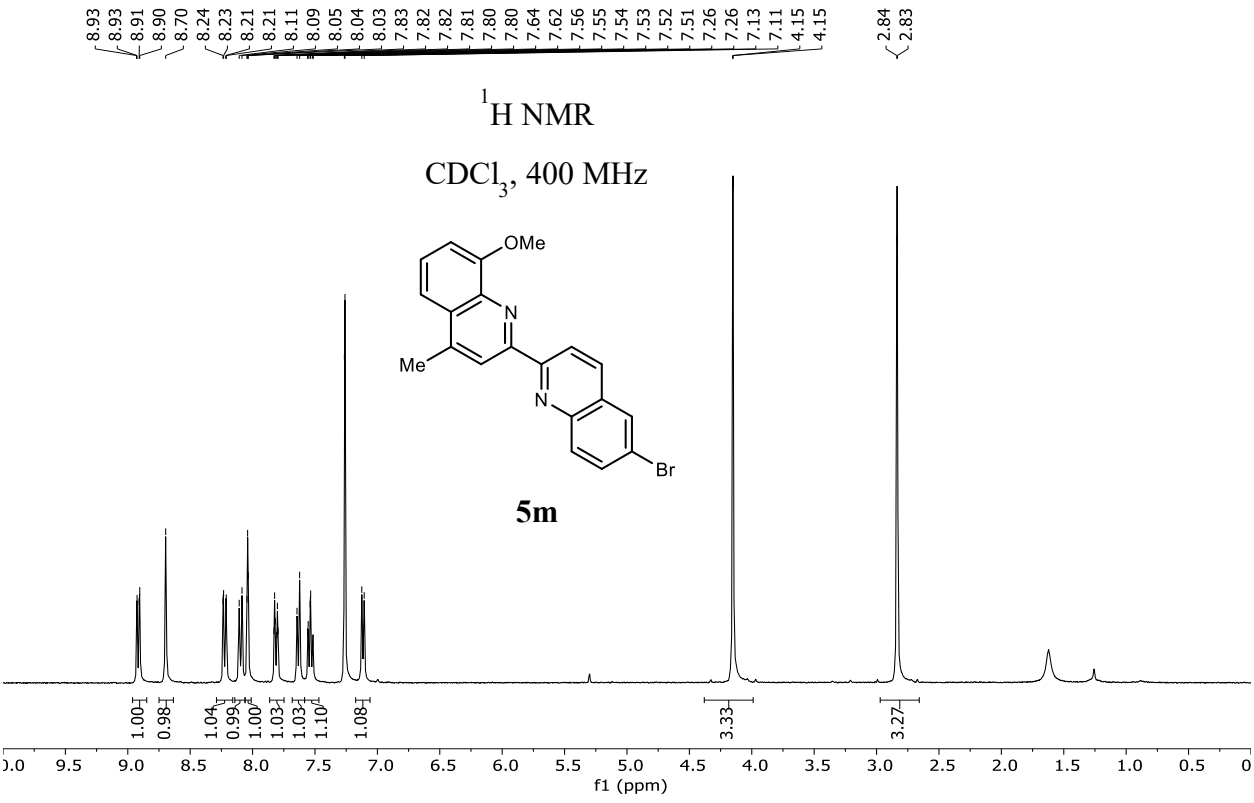
^{13}C NMR

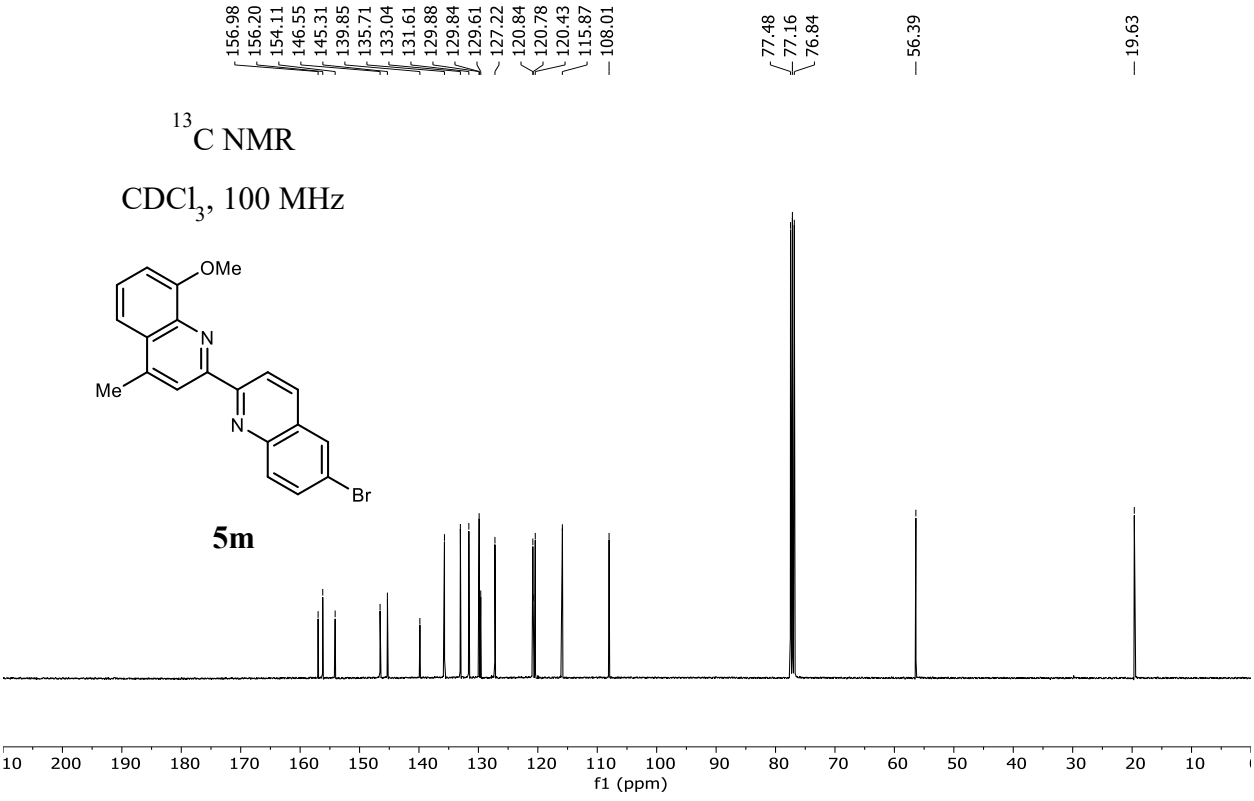
$CDCl_3$, 100 MHz

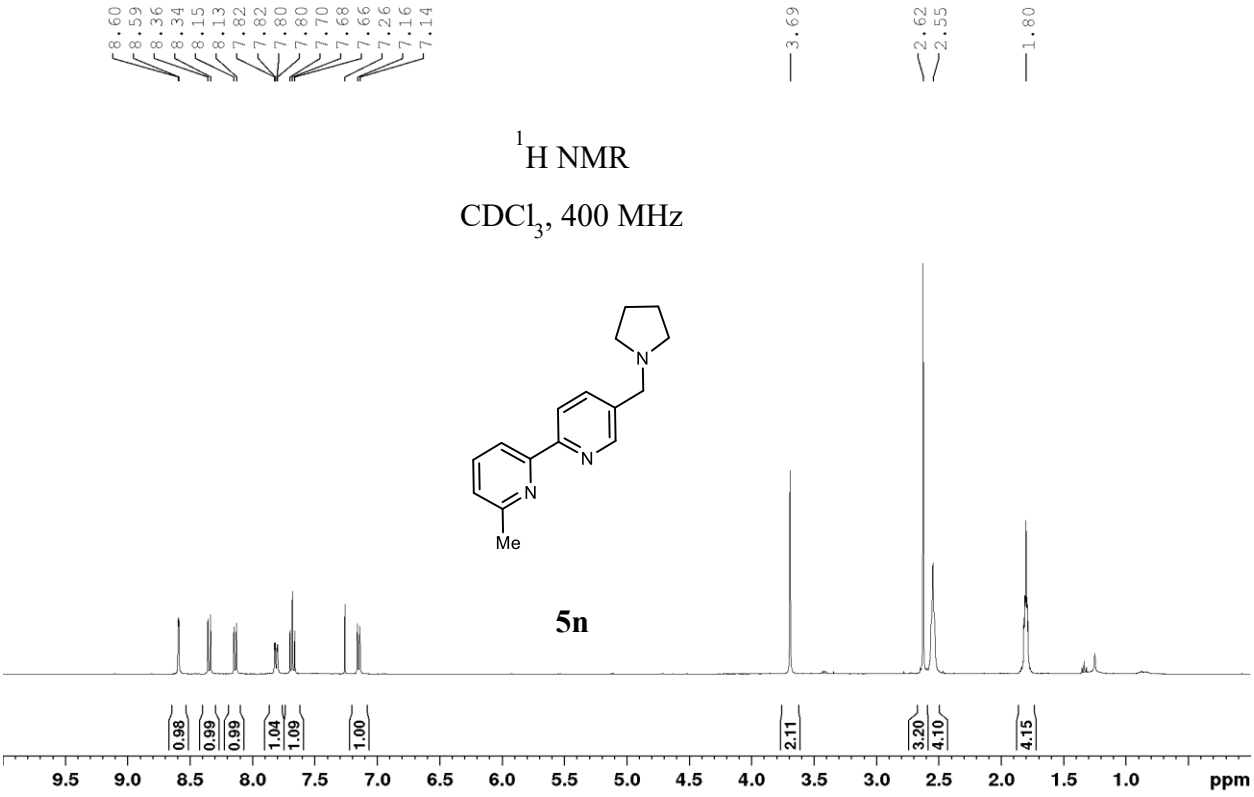
5k


9.34
8.89
8.21
7.42
7.26
4.09
4.01
2.85
2.83
2.81
2.79
1.42
1.40
1.38
^{1}H NMR
$CDCl_3$, 400 MHz
MeO
MeO
N
N
N
N
5l
0.950
1.840
0.978
0.988
3.026
3.060
2.069
3.090
f1 (ppm)


162.17
159.01
157.11
156.10
153.74
151.00
150.59
136.57
119.11
107.05
104.37
77.48
77.16
76.84
56.55
56.25
23.77
14.92
^{13}C NMR
$CDCl_3$, 100 MHz
MeO
MeO
N
N
N
N
5l
f1 (ppm)


8.93
8.93
8.91
8.90
8.70
8.24
8.23
8.21
8.21
8.11
8.09
8.05
8.04
8.03
7.83
7.82
7.82
7.81
7.80
7.80
7.64
7.62
7.56
7.55
7.54
7.53
7.52
7.51
7.26
7.26
7.13
7.11
4.15
4.15
2.84
2.83
1H NMR
CDCl3, 400 MHz
OMe
N
Me
N
Br
5m
1.00
0.98
1.04
0.99
1.00
1.03
1.03
1.10
1.08
3.33
3.27
f1 (ppm)

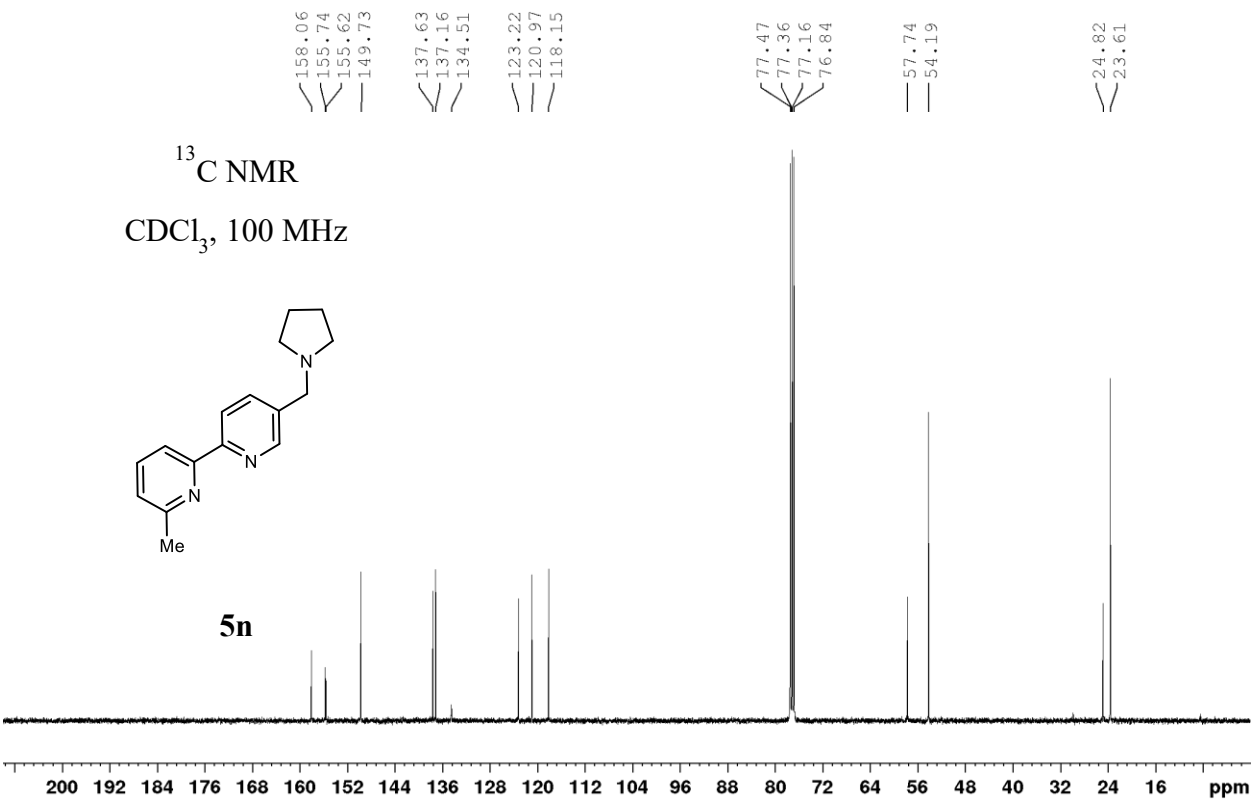

156.98
156.20
154.11
146.55
145.31
139.85
135.71
133.04
131.61
129.88
129.84
129.61
127.22
120.84
120.78
120.43
115.87
108.01
77.48
77.16
76.84
56.39
19.63
13C NMR
CDCl3, 100 MHz
OMe
N
Me
N
Br
5m
f1 (ppm)



^{1}H NMR

$CDCl_3$, 400 MHz

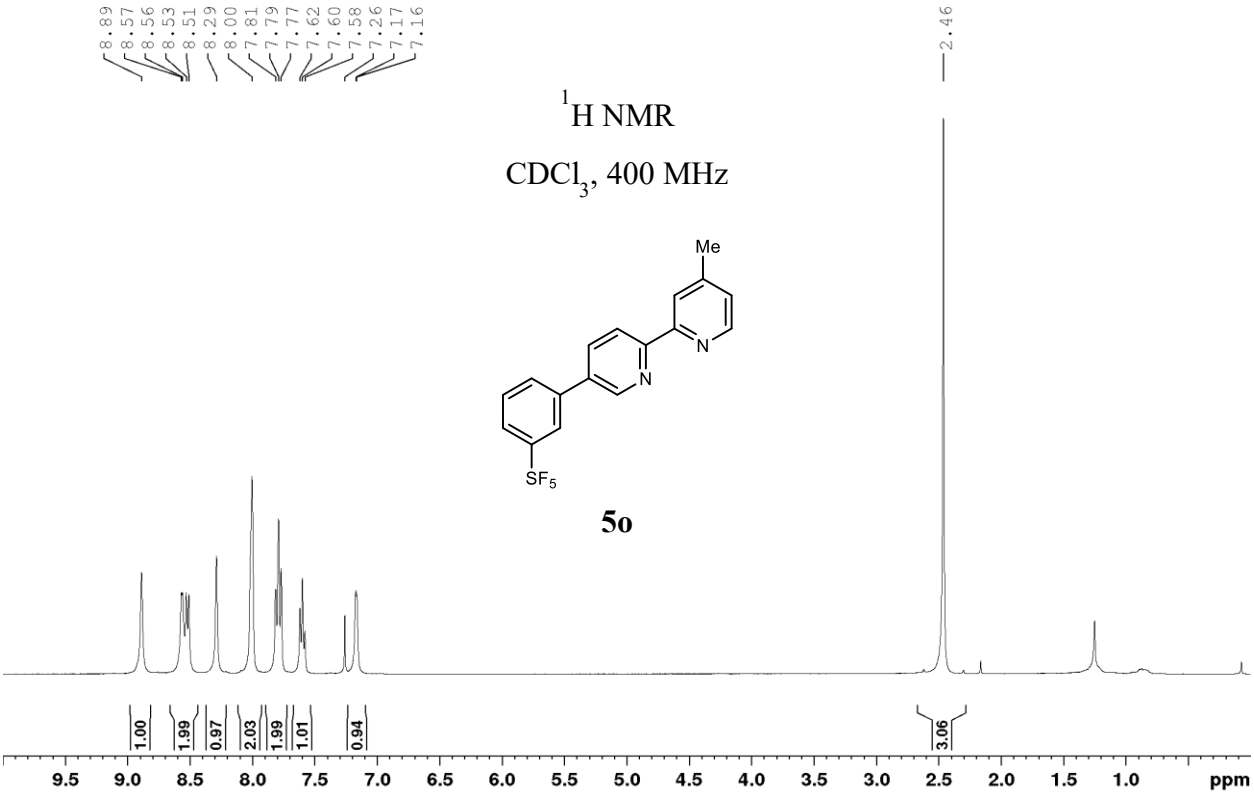
5n

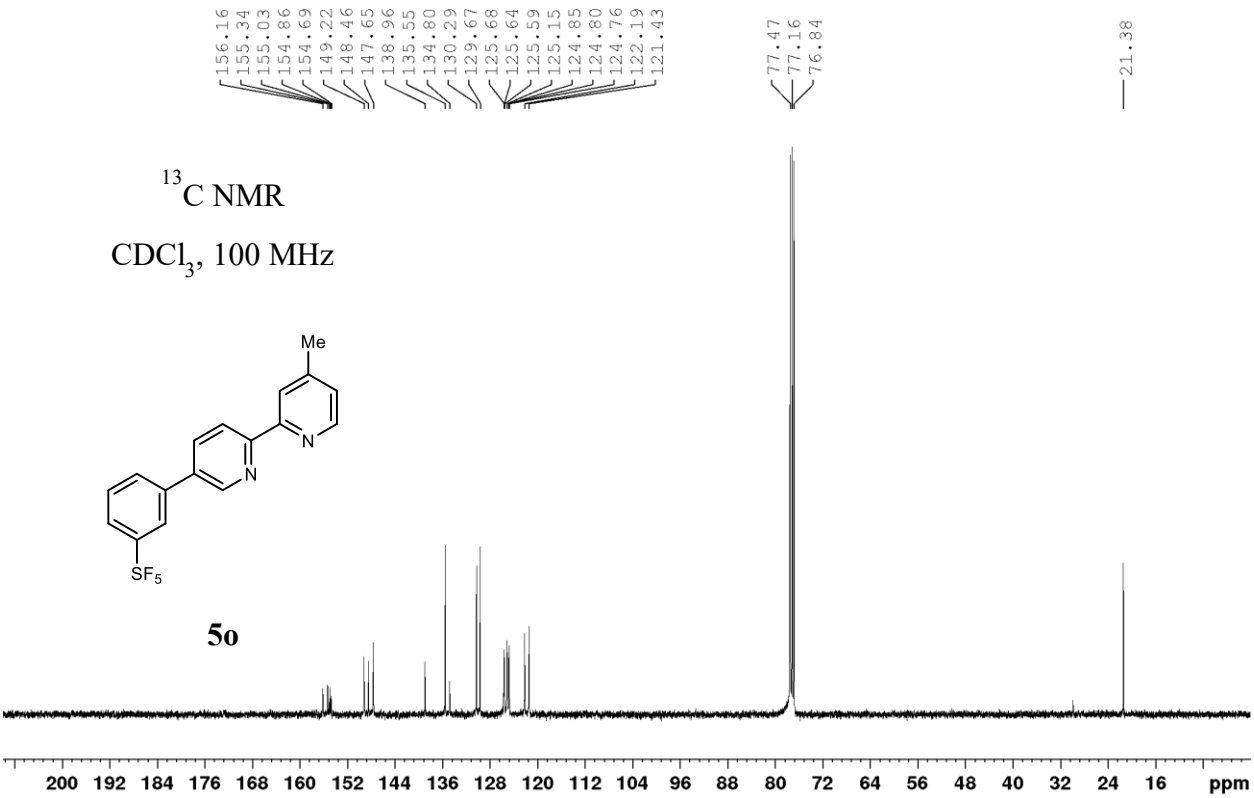


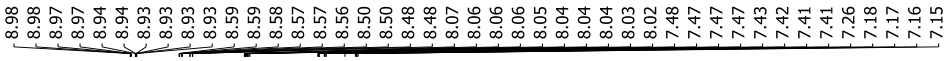
^{13}C NMR

$CDCl_3$, 100 MHz

5n

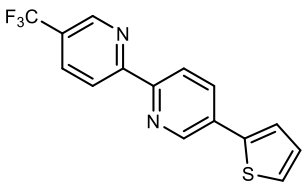

8.89
8.57
8.56
8.53
8.51
8.29
8.00
7.81
7.79
7.77
7.62
7.60
7.58
7.26
7.17
7.16
2.46
1H NMR
CDCl3, 400 MHz
Me
N
N
SF5
5o
1.00
1.99
0.97
2.03
1.99
1.01
0.94
3.06
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


156.16
155.34
155.03
154.86
154.69
149.22
148.46
147.65
138.96
135.55
134.80
130.29
129.67
125.68
125.64
125.59
125.15
124.85
124.80
124.76
122.19
121.43
77.47
77.16
76.84
21.38
13C NMR
CDCl3, 100 MHz
Me
N
N
SF5
5o
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

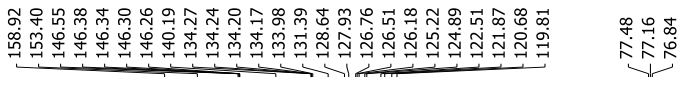


^{1}H NMR

$CDCl_3$, 400 MHz

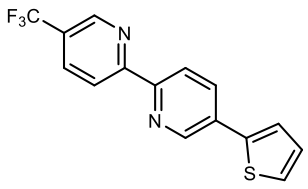


5p

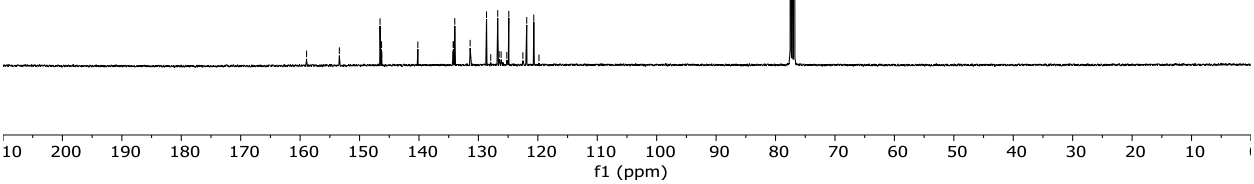


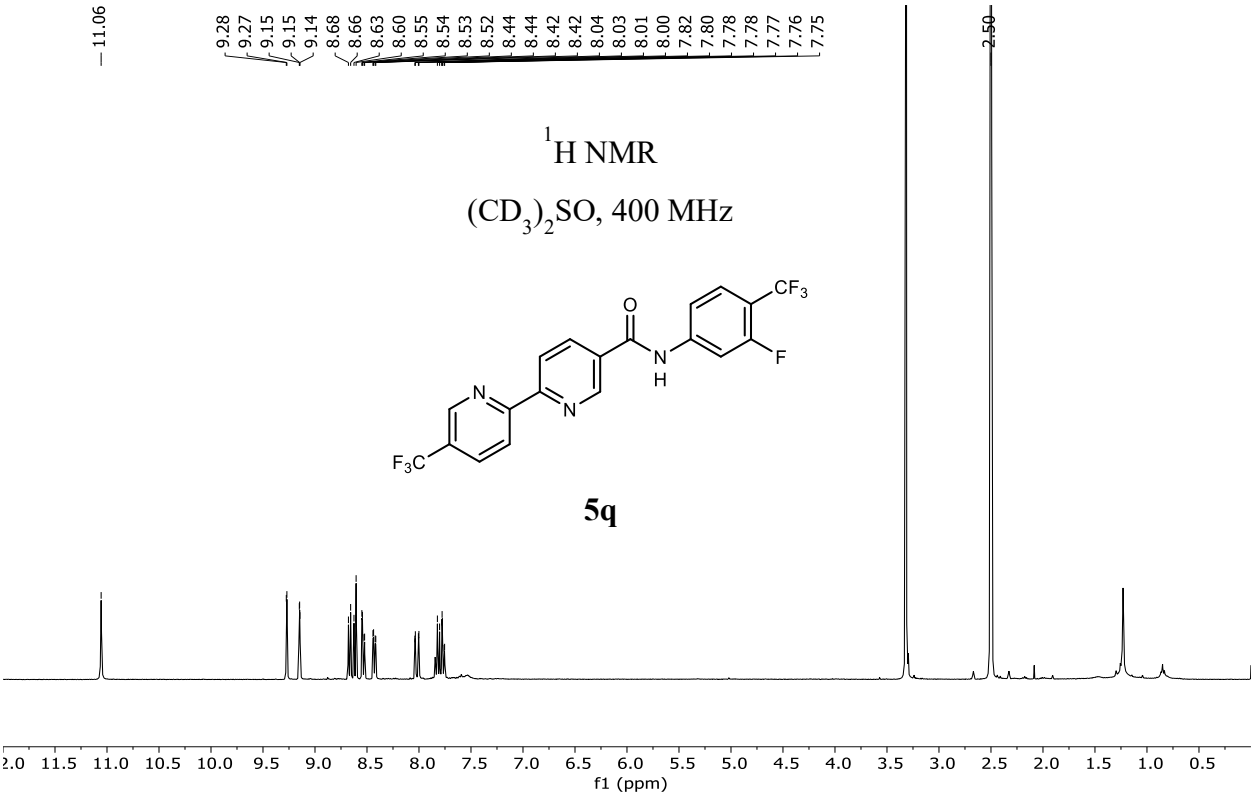
^{13}C NMR

$CDCl_3$, 100 MHz



5p

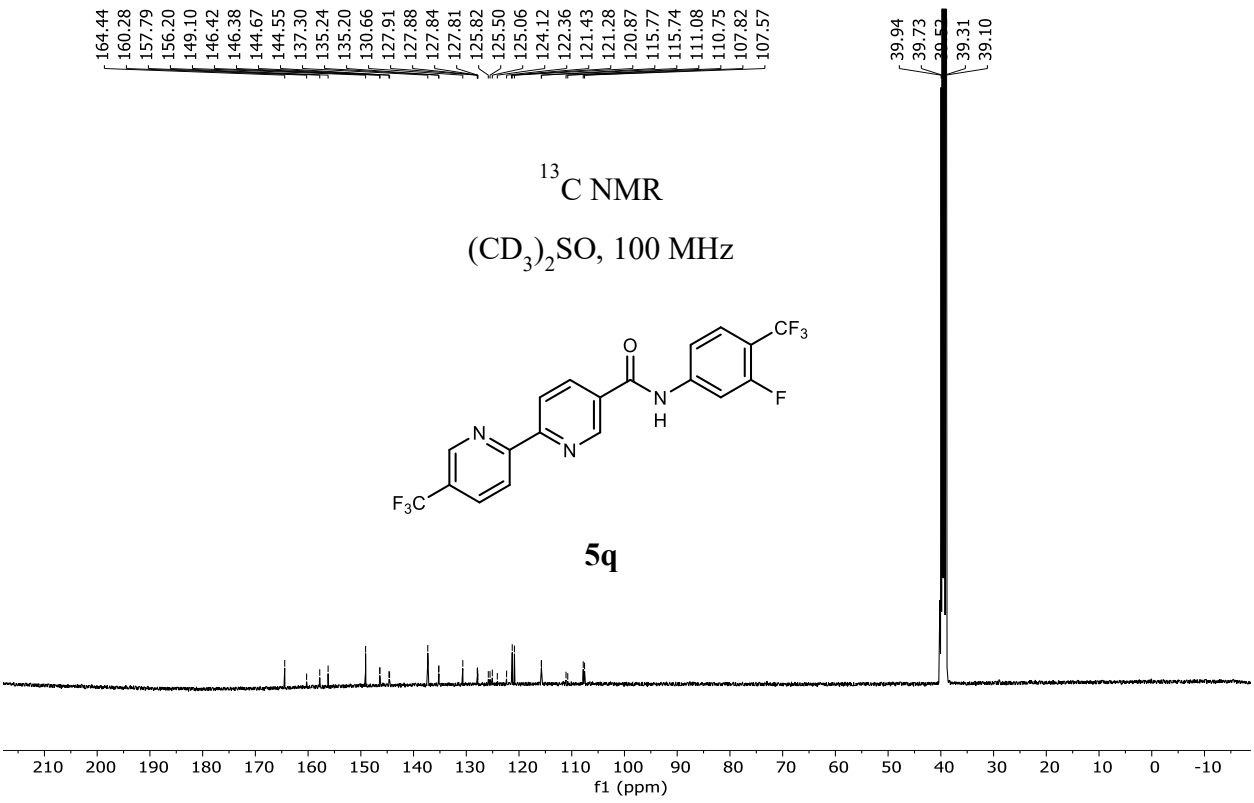




^{1}H NMR

$(CD_3)_2SO$, 400 MHz

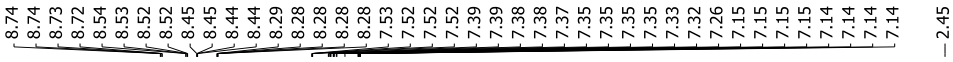
5q



^{13}C NMR

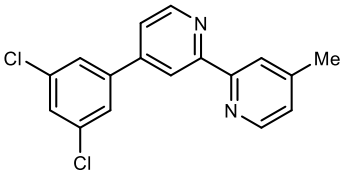
$(CD_3)_2SO$, 100 MHz

5q



^{1}H NMR

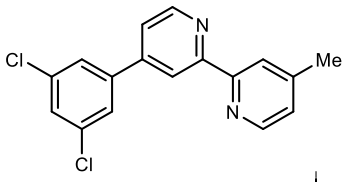
$CDCl_3$, 400 MHz



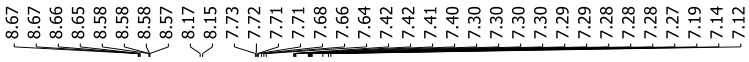
5r

^{13}C NMR

$CDCl_3$, 100 MHz

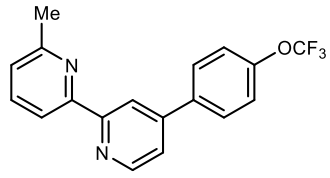


5r

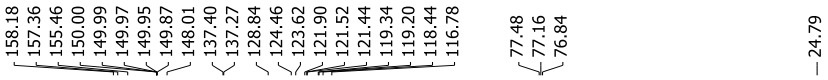


^{1}H NMR

$CDCl_3$, 400 MHz

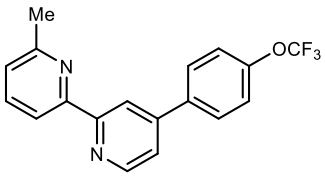


5s

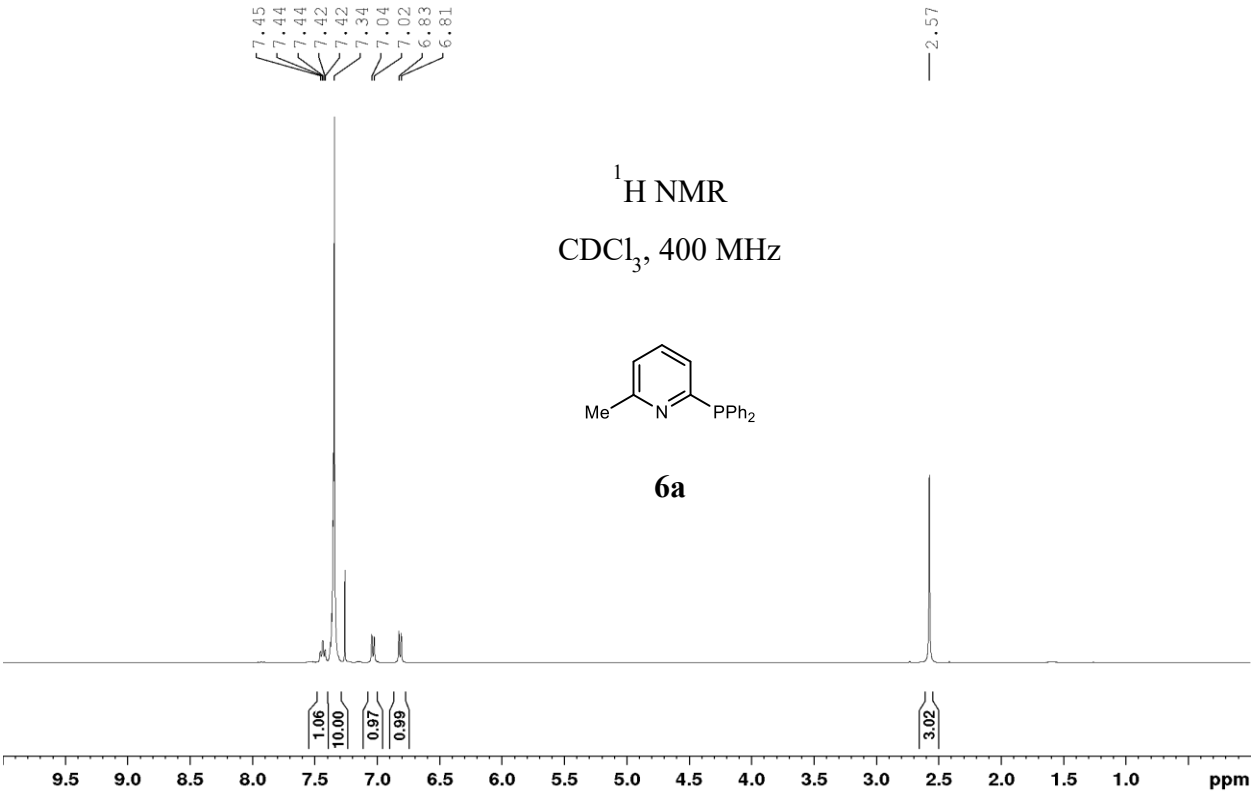


^{13}C NMR

$CDCl_3$, 100 MHz



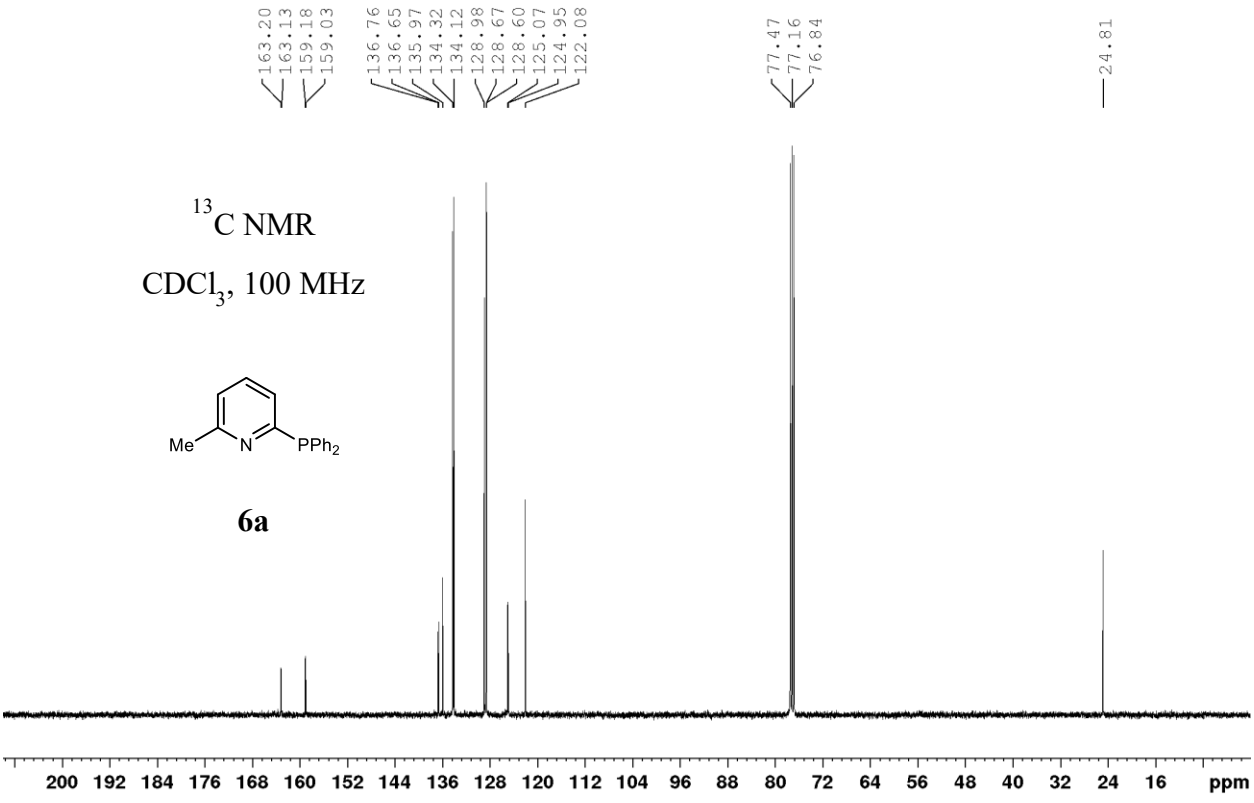
5s



^{1}H NMR

$CDCl_3$, 400 MHz

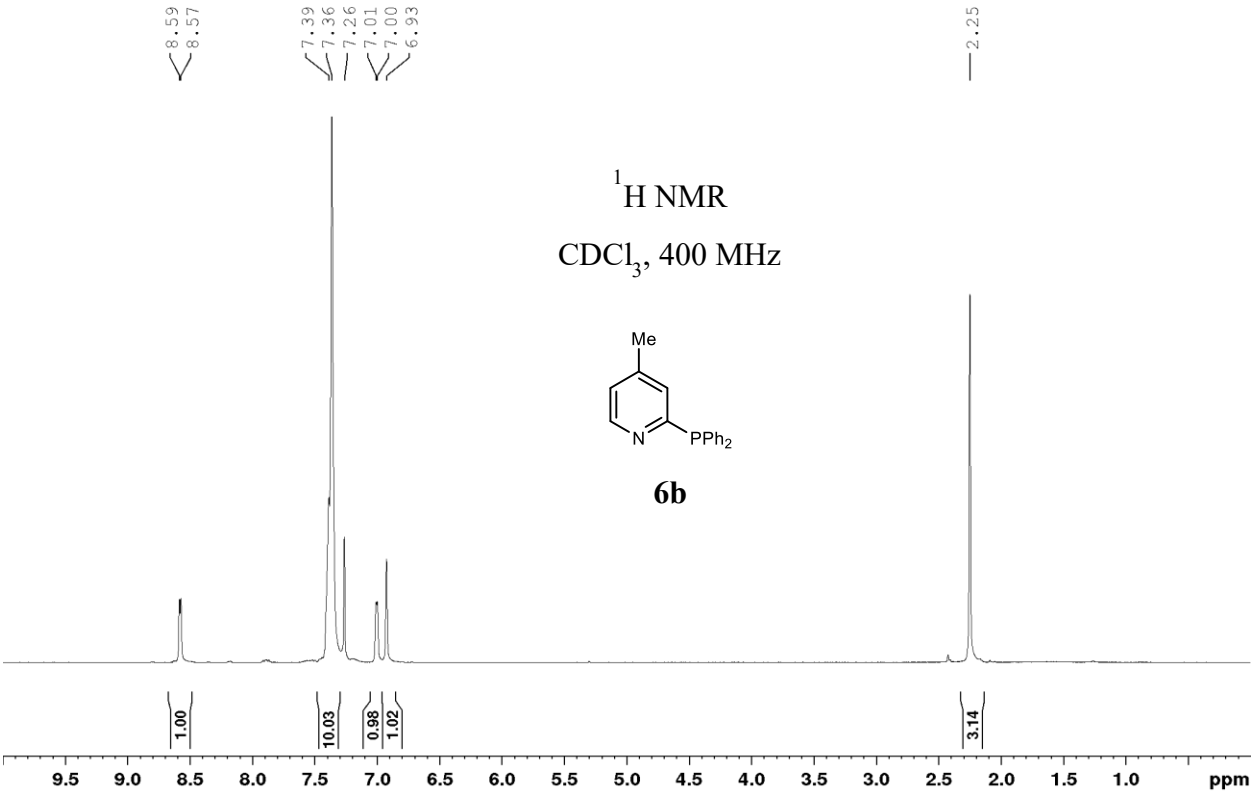
6a



^{13}C NMR

$CDCl_3$, 100 MHz

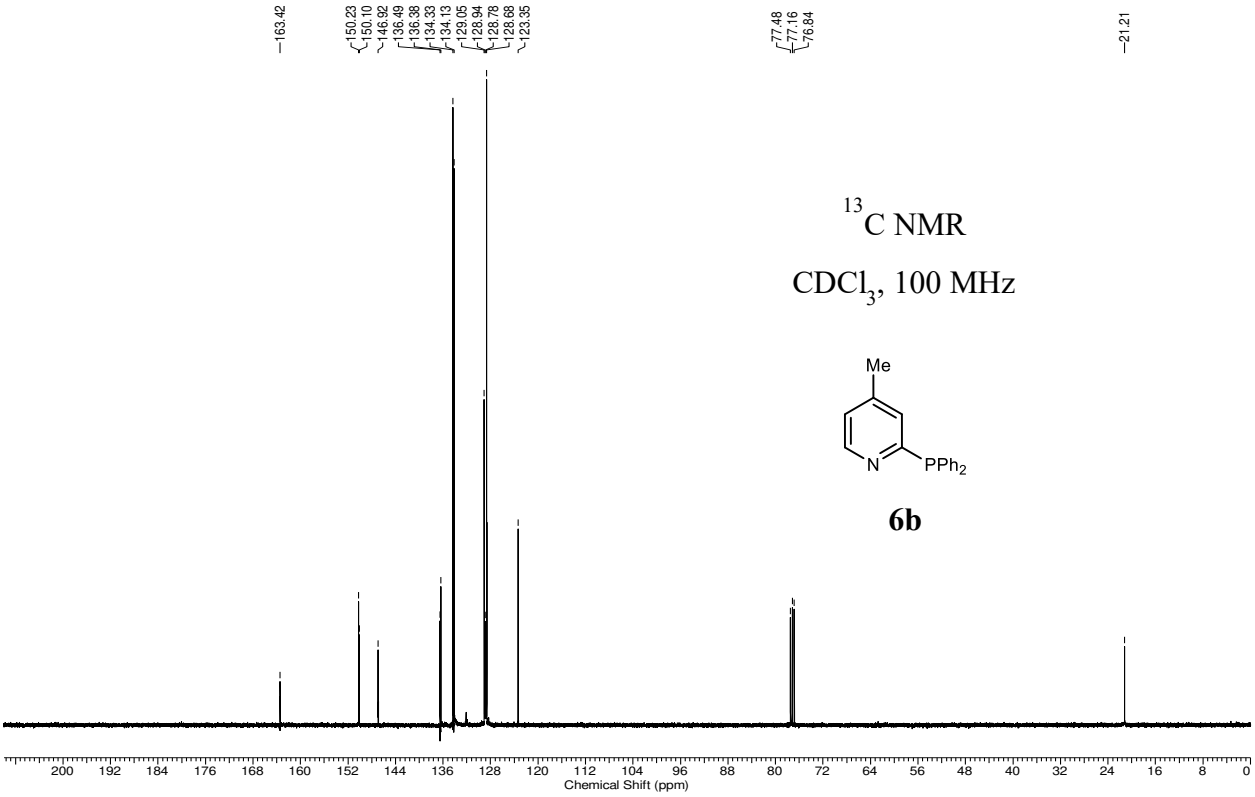
6a



^{1}H NMR

$CDCl_3$, 400 MHz

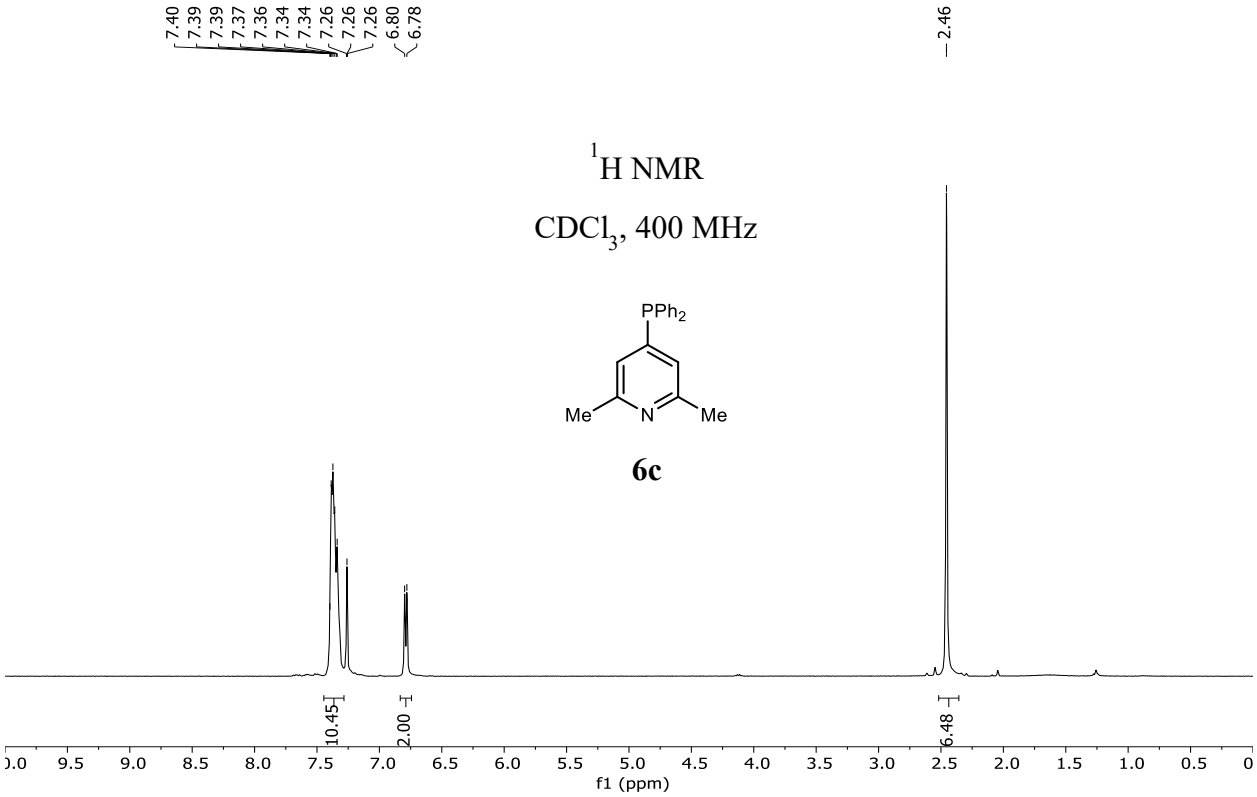
6b



^{13}C NMR

$CDCl_3$, 100 MHz

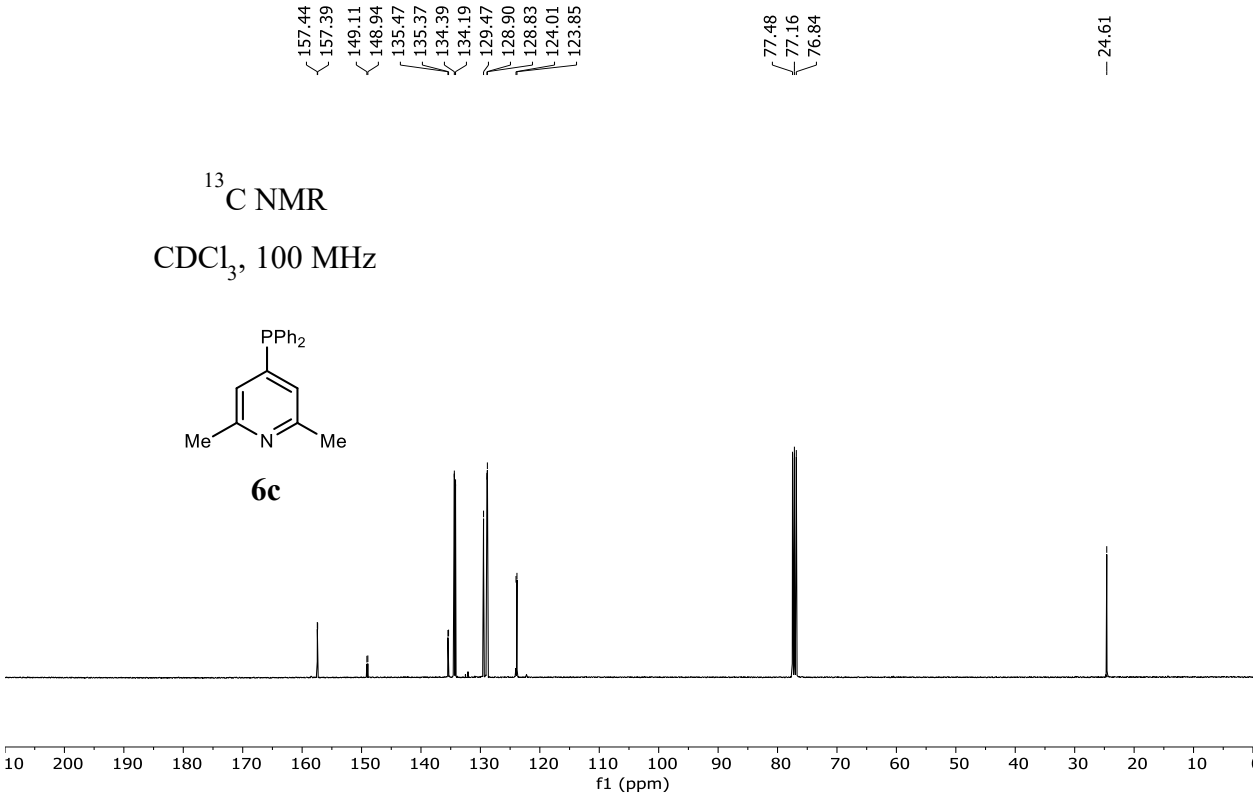
6b



^{1}H NMR

$CDCl_3$, 400 MHz

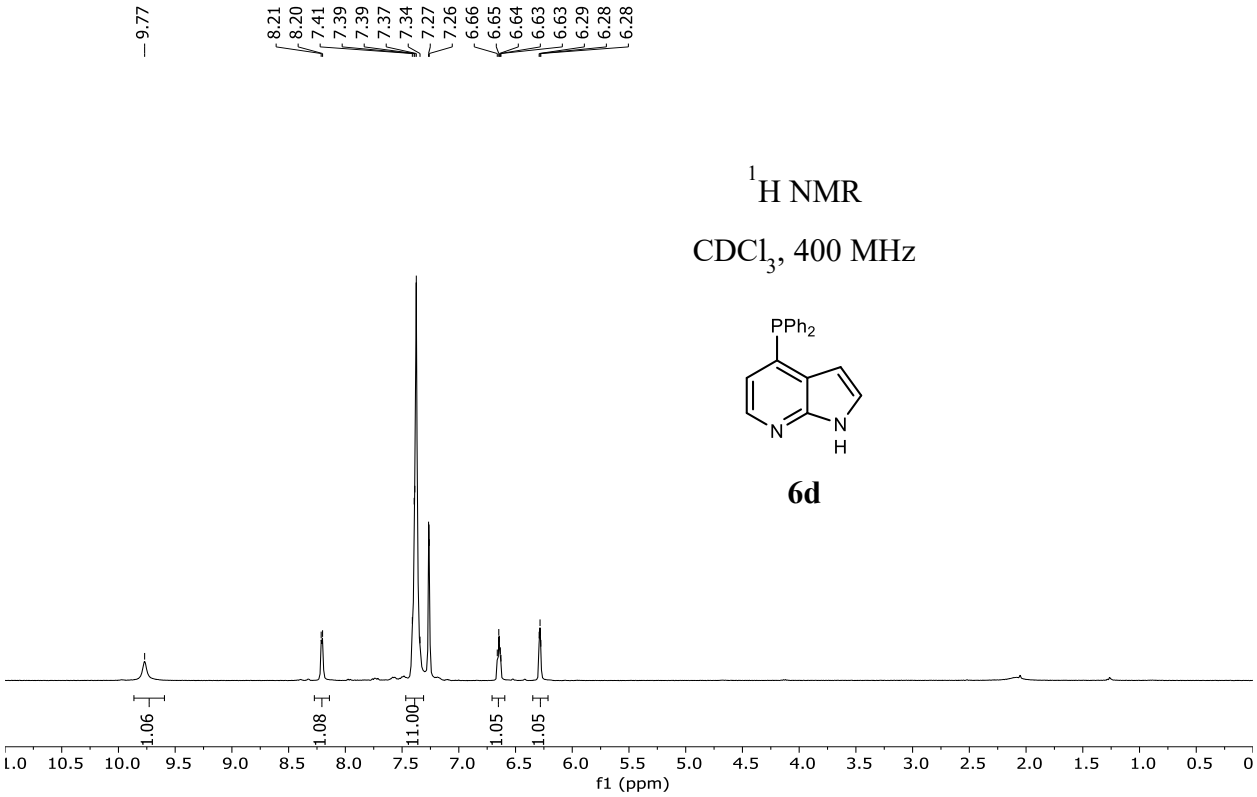
6c

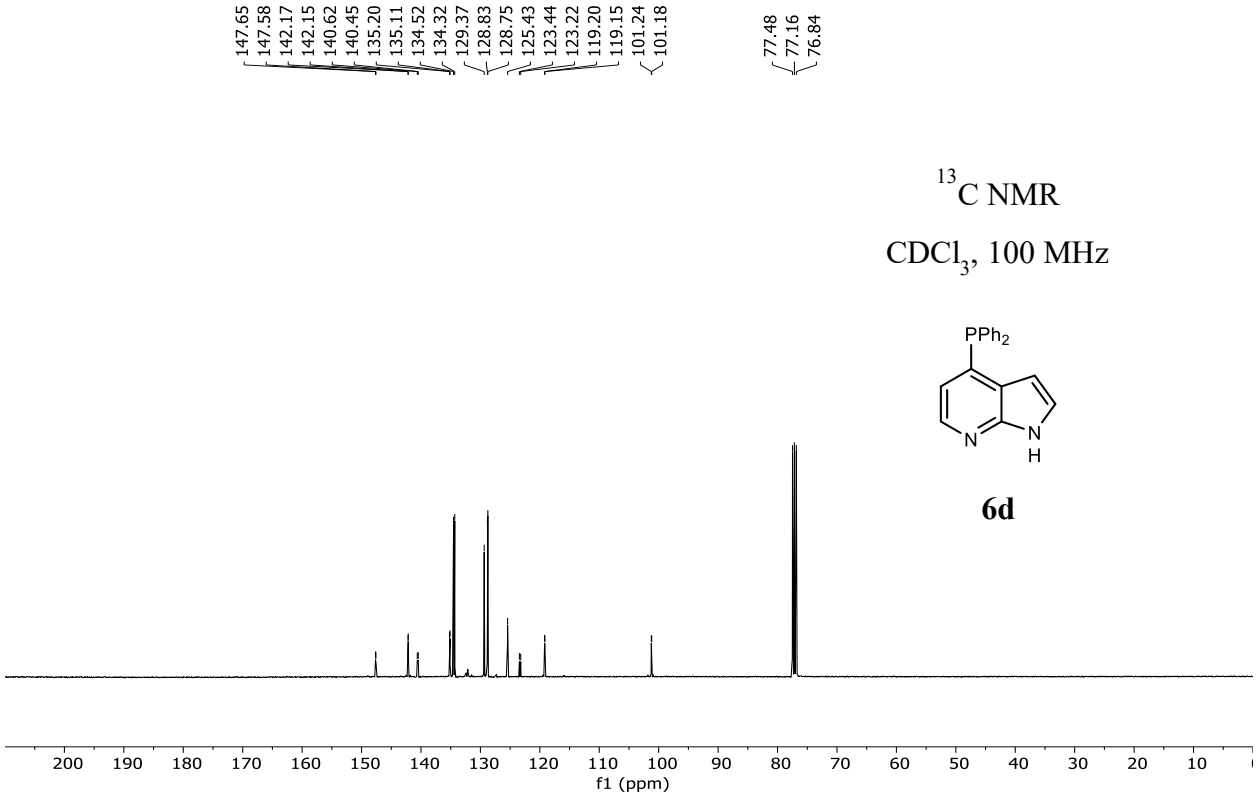


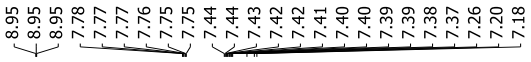
^{13}C NMR

$CDCl_3$, 100 MHz

6c

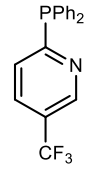

9.77
8.21
8.20
7.41
7.39
7.39
7.37
7.34
7.27
7.26
6.66
6.65
6.64
6.63
6.63
6.29
6.28
6.28
1H NMR
CDCl3, 400 MHz
PPh2
N
N
H
6d
1.06
1.08
11.00
1.05
1.05
f1 (ppm)


147.65
147.58
142.17
142.15
140.62
140.45
135.20
135.11
134.52
134.32
129.37
128.83
128.75
125.43
123.44
123.22
119.20
119.15
101.24
101.18
77.48
77.16
76.84
13C NMR
CDCl3, 100 MHz
PPh2
N
N
H
6d
f1 (ppm)

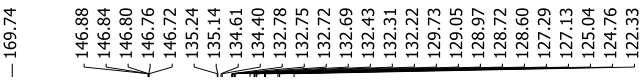


^{1}H NMR

$CDCl_3$, 400 MHz

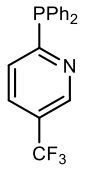


6e

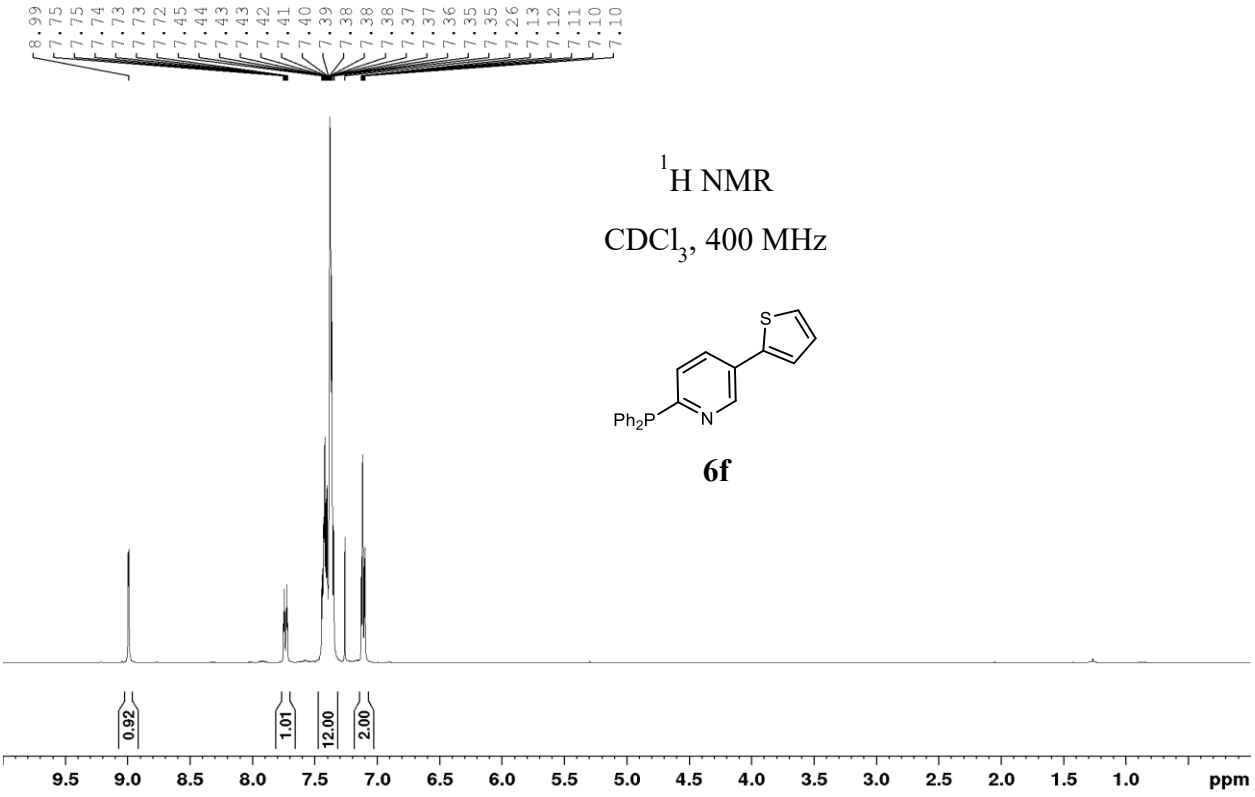


^{13}C NMR

$CDCl_3$, 100 MHz



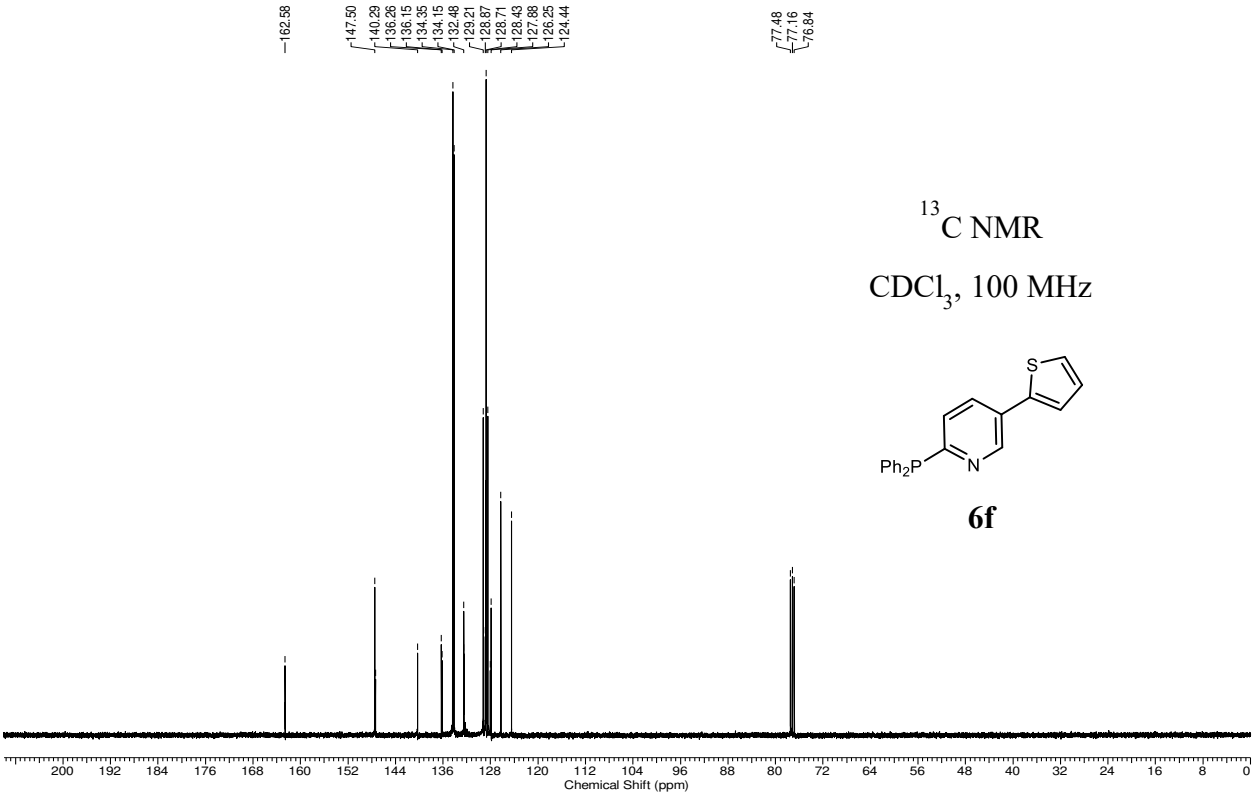
6e



^{1}H NMR

$CDCl_3$, 400 MHz

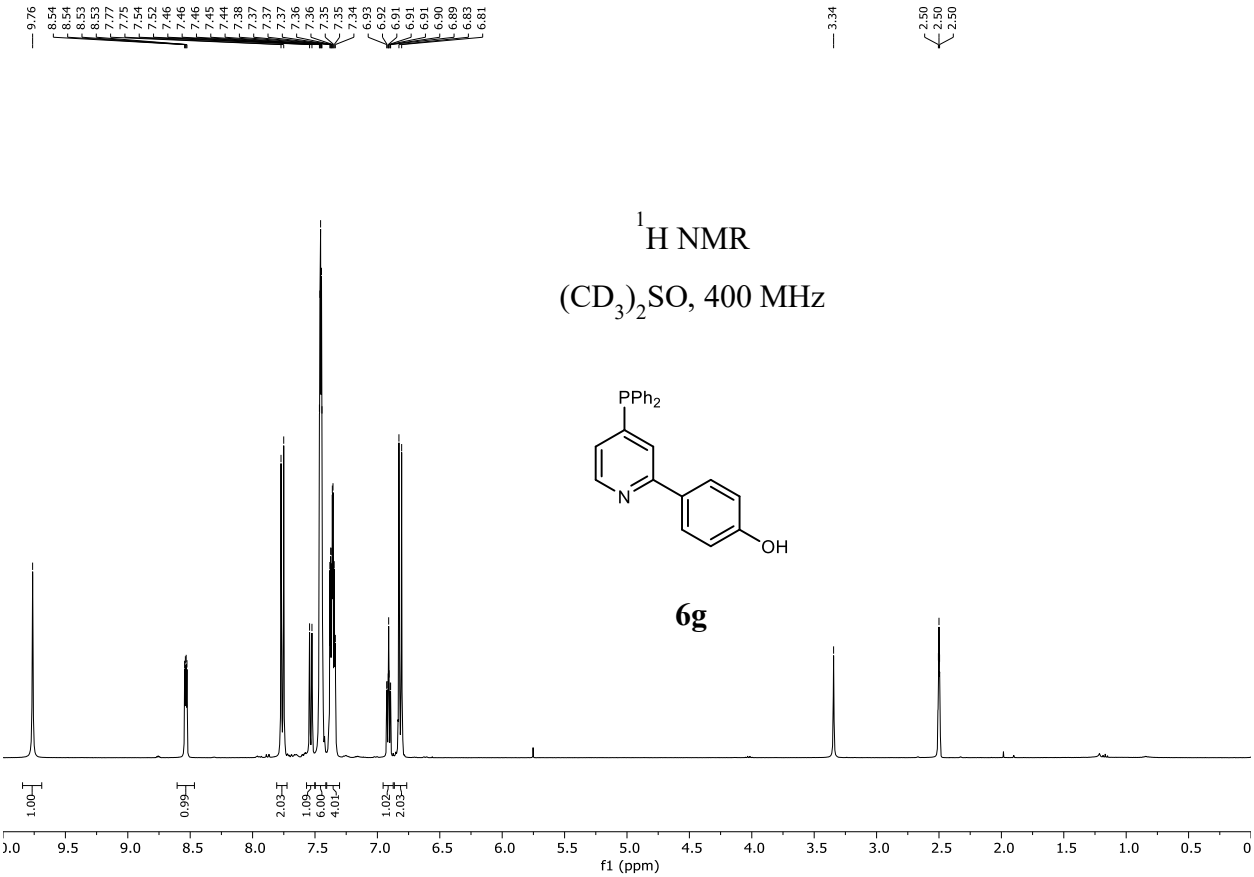
6f

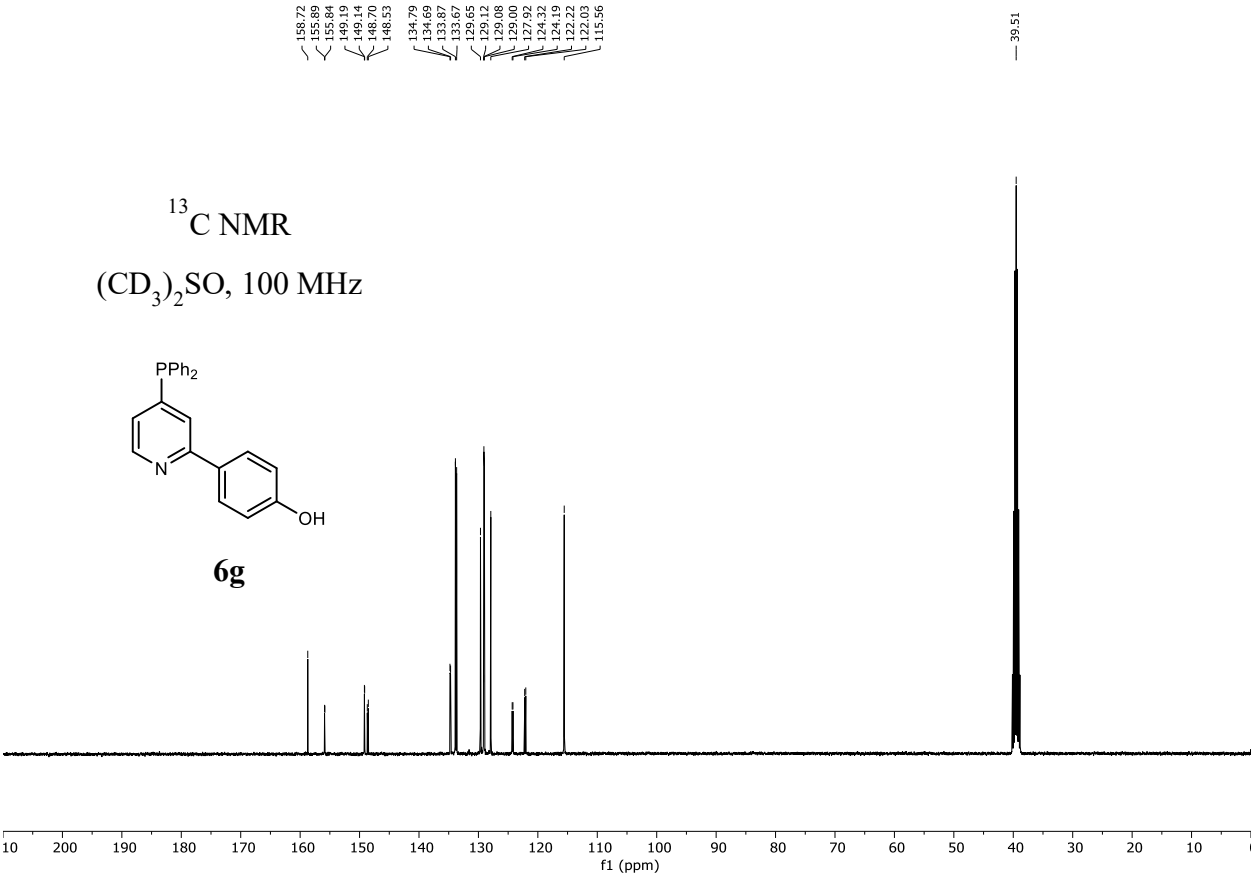


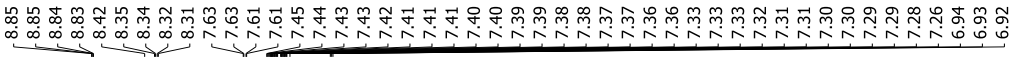
^{13}C NMR

$CDCl_3$, 100 MHz

6f

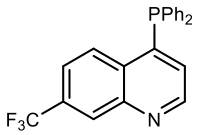

9.76
8.54
8.54
8.53
8.53
7.77
7.75
7.54
7.52
7.46
7.46
7.46
7.45
7.44
7.38
7.37
7.37
7.37
7.36
7.36
7.35
7.35
7.34
6.93
6.92
6.91
6.91
6.91
6.90
6.89
6.83
6.81
3.34
2.50
2.50
2.50
1H NMR
(CD3)2SO, 400 MHz
PPh2
N
OH
6g
1.00
0.99
2.03
1.09
6.00
4.01
1.02
2.03
f1 (ppm)


158.72
155.89
155.84
149.19
149.14
146.70
146.53
134.79
134.69
133.87
133.67
129.65
129.12
129.08
129.00
127.92
124.32
124.19
122.22
122.03
115.56
39.51
13C NMR
(CD3)2SO, 100 MHz
PPh2
N
OH
6g
f1 (ppm)

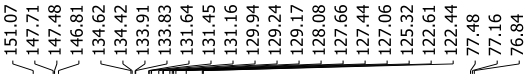


^{1}H NMR

$CDCl_3$, 400 MHz

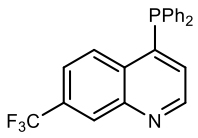


6h

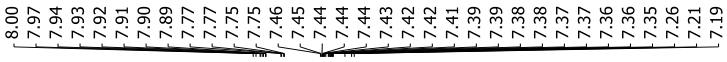


^{13}C NMR

$CDCl_3$, 100 MHz

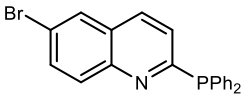


6h

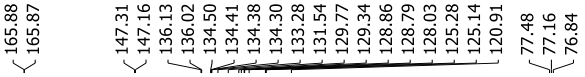


^{1}H NMR

$CDCl_3$, 400 MHz

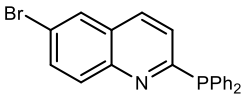


6i



^{13}C NMR

$CDCl_3$, 100 MHz

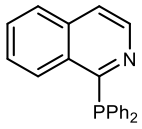


6i

8.64 8.63 8.62 8.61 8.60 8.59 7.83 7.81 7.67 7.67 7.65 7.65 7.65 7.63 7.63 7.58 7.57 7.54 7.53 7.52 7.52 7.51 7.50 7.50 7.44 7.44 7.43 7.42 7.42 7.41 7.40 7.40 7.39 7.38 7.36 7.35 7.35 7.34 7.33 7.33 7.33 7.32 7.32 7.31 7.31 7.30 7.26

^{1}H NMR

$CDCl_3$, 400 MHz

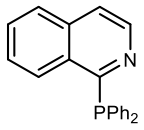


6j

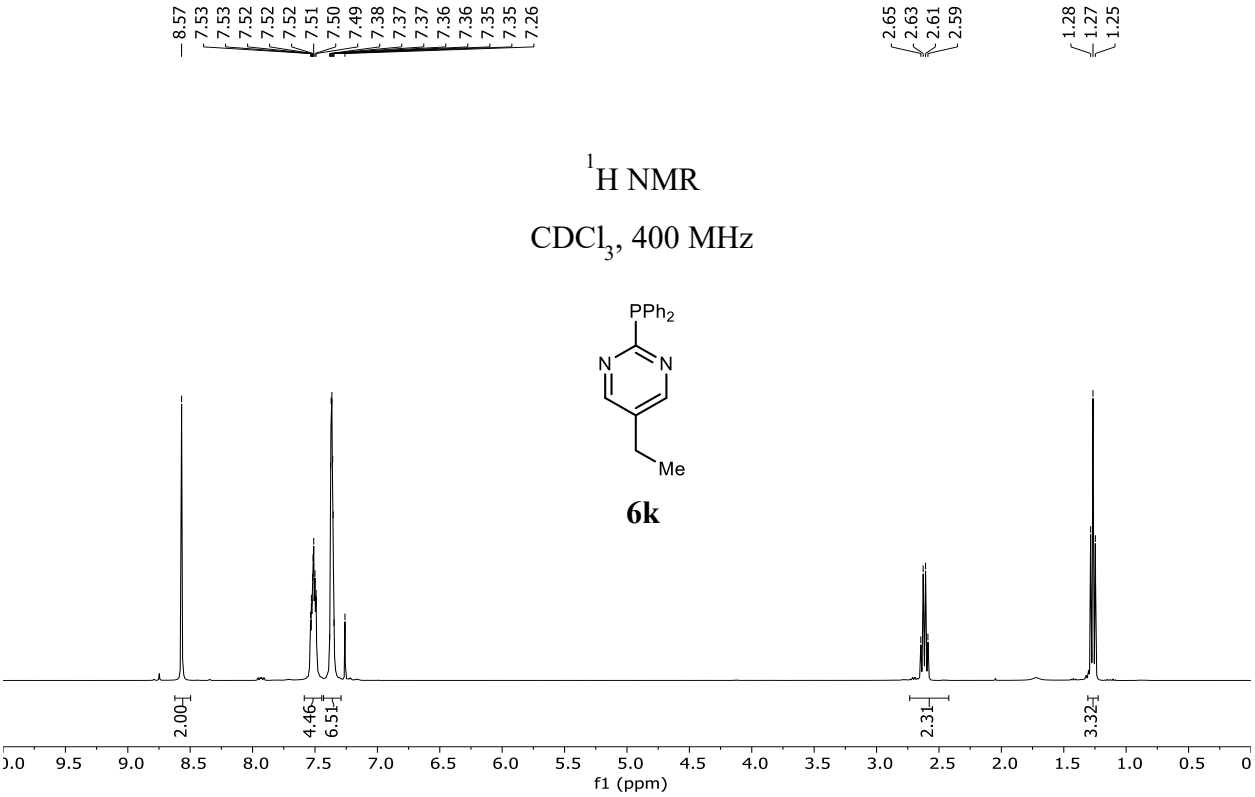
163.88 163.78 143.43 143.39 136.16 136.09 135.54 135.50 134.74 134.54 132.37 132.09 130.14 130.13 129.01 128.54 128.47 127.47 127.45 127.28 127.26 127.16 126.94 120.50 77.48 77.16 76.84

^{13}C NMR

$CDCl_3$, 100 MHz



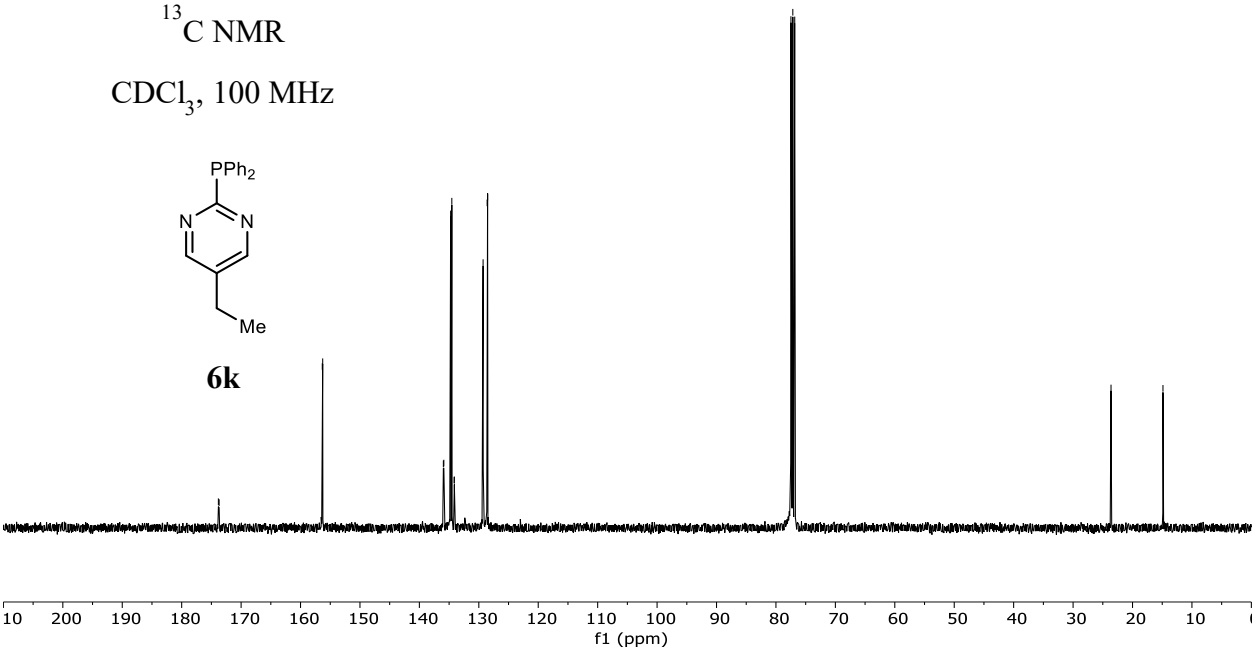
6j



^{1}H NMR

$CDCl_3$, 400 MHz

6k



^{13}C NMR

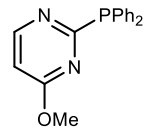
$CDCl_3$, 100 MHz

6k

8.41 8.41 8.40 8.40 7.55 7.55 7.55 7.54 7.54 7.53 7.53 7.53 7.53 7.52 7.52 7.51 7.51 7.51 7.51 7.50 7.38 7.37 7.37 7.37 7.36 7.36 7.35 7.35 7.35 7.34 7.34 7.34 7.26 6.54 6.54 6.53 6.53 3.75

^{1}H NMR

$CDCl_3$, 400 MHz

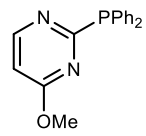


6l

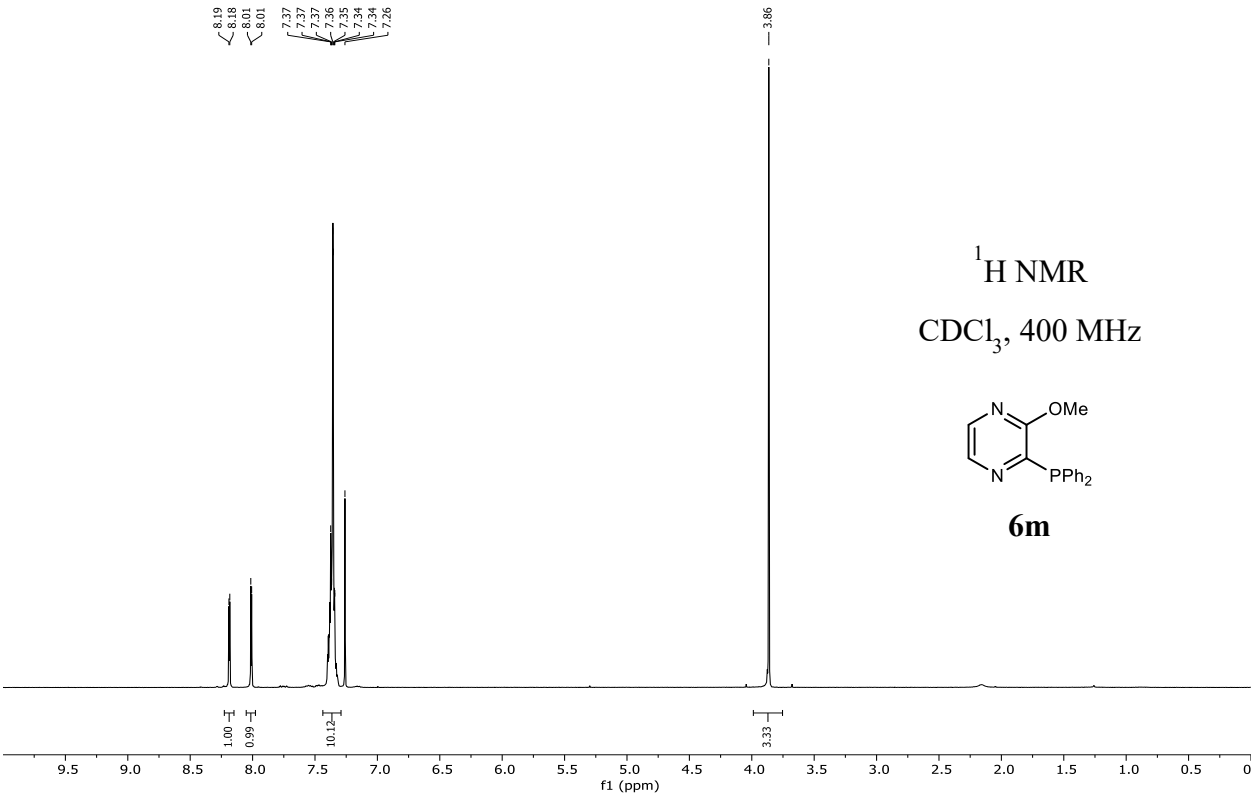
175.90 175.78 168.11 168.04 156.70 156.62 135.56 135.49 134.64 134.44 128.97 128.18 128.10 105.99 105.97 77.32 77.00 76.68 53.51

^{13}C NMR

$CDCl_3$, 100 MHz



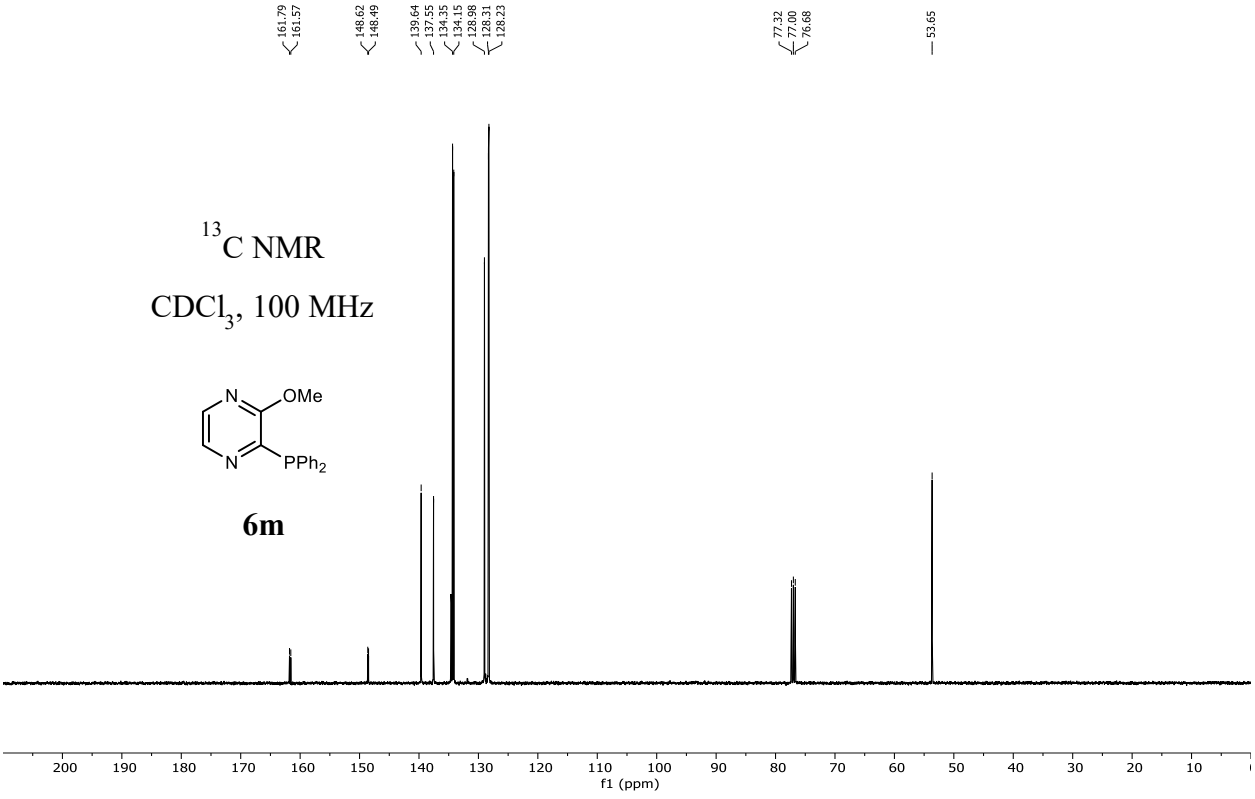
6l



^{1}H NMR

$CDCl_3$, 400 MHz

6m



^{13}C NMR

$CDCl_3$, 100 MHz

6m